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Methods for the Construction of *trans*-Hydrindane Rings and their Origins in Steroid Chemistry. Vitamin D Total Synthesis

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1. Introduction

The construction of the *trans*-hydrindane portion of steroids,[1] vitamin D,[2] higher terpenes and related natural products[3] has received a great deal of attention. Many methods have been developed for stereoselective generation of two chiral centres that ultimately correspond to the carbon atoms C_{13} and C_{14} in the cholestane skeleton. Most of these methods involve intermediates in which the chiral centre at C_{13} has been already established. Construction of the chiral centre at C_{14} is then based upon reactions of the double bond located at carbon C_{14} (C_8-C_{14} or C_{14}-C_{15}). Interesting parallels can be found in the reactivity of hydrindane building blocks and more complex polycyclic systems including condensed six- and five membered rings. Transformations of the AB rings of cholestane,[4] which probably is the most studied natural decalin derivative, are also of relevance. This review presents methods for the construction of the *trans*-hydrindane ring system in the context of steroid chemistry and total synthesis. The literature is included up to the end of 1996.

2. Catalytic hydrogenation of precursors with a double bond at the ring junction

2.1. Heterogeneous catalytic hydrogenation

Catalytic hydrogenation of cholest-4-ene over heterogeneous palladium or platinum catalysts in a neutral medium affords primarily 5β-cholestane. However, in acetic acid 5α-isomer is formed exclusively, presumably due to migration of the double bond into 5,6 position. Hydrogenation of cholest-5-ene affords exclusively the 5α-product.[5,6]

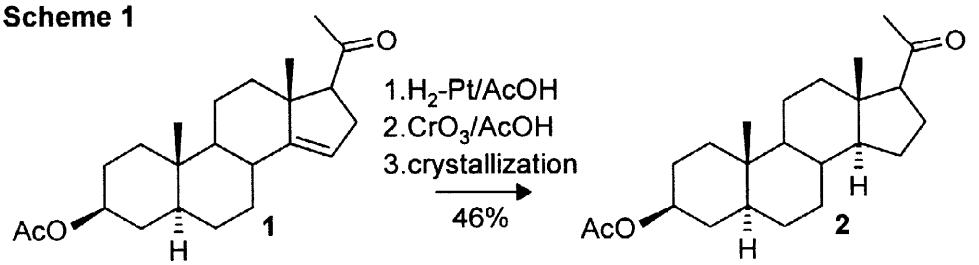
Steroids with 3-oxo-4-ene function on catalytic hydrogenation over palladium or platinum catalysts in polar solvents under neutral conditions yield mixtures of isomers, but almost exclusively 5β-isomer in basic media.[7] Addition of acid also increases the proportion of 5β-isomer (for example HBr-AcOH).[8] Recently, it has been reported that the Cu/Al_2O_3 catalyst may also be used with the same stereochemical outcome.[9] Typical examples of unsaturated ketones hydrogenation are presented in Table 1.

Table 1.

Typical examples of catalytic hydrogenation of steroid 4-ene-3-ones.

	catalyst/solvent	yield	*cis/trans* ratio	Ref.
cholest-4-en-3-one	Pt/hexane	100%	**71**: **29**	10
testosterone	Pd-$CaCO_3$/ethanol	68%	**66**: **34**	11
testosterone	Pd-$CaCO_3$/propan-2-ol	92%	**52**: **48**	11
testosterone	Pd-$CaCO_3$/cyclohexane	68 %	**34**: **66**	11
androst-4-en-3,17-dione	Pd-C/AcOEt	100%	**69**: **31**	12

Scheme 1

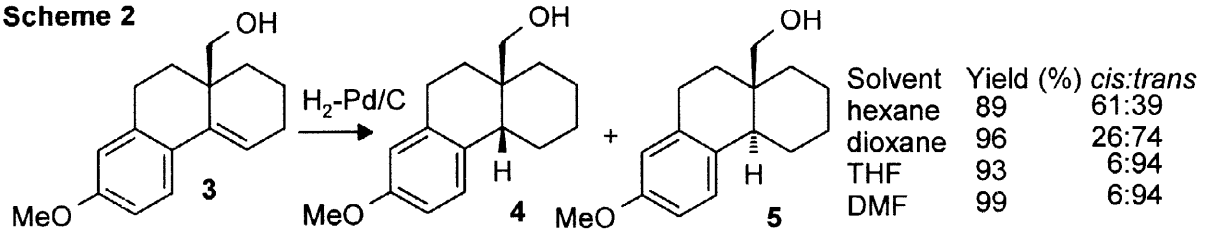


The first (to the best of our knowledge) report[13] on the stereochemistry of 15-ene hydrogenation (**1**, Scheme

1) may suggest that the corresponding 15α-H derivative has been formed exclusively. However, the characterized product (**2**) was purified by crystallization and its yield amounted to 46% only.

Polar functional groups present in the molecule may exert potent directing effect upon the steric course of catalytic hydrogenation. Instructive examples are given in the work of Thompson *et al.*[14] Homoallylic alcohol **3** (Scheme 2) was hydrogenated over palladium-on-carbon or platinum catalysts in various solvents. It was found that in non-polar solvents the *cis*-product **4** predominates whereas with an increase of the solvent dielectric constant the proportion of the *trans*-isomer **5** increases. Some of the reported results are included in Scheme 2 .

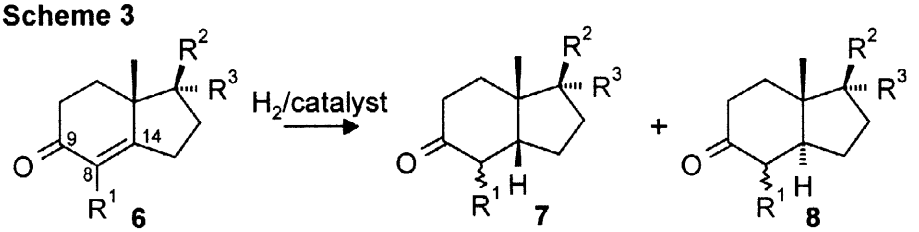
Scheme 2



Solvent	Yield (%)	*cis:trans*
hexane	89	61:39
dioxane	96	26:74
THF	93	6:94
DMF	99	6:94

The bicyclic α,β-unsaturated ketones related to hydrindane (9-oxo-8(14)-enes) appear to have a high preference for formation of the respective *cis*-fused products upon catalytic hydrogenation.[15-17] However, stereoselective addition of hydrogen affording *trans*-fused hydrindanes preferentially or exclusively was achieved using compounds with a large substituent at C_8. Some representative results [17] are presented in Scheme 3 and Table 2.

Scheme 3



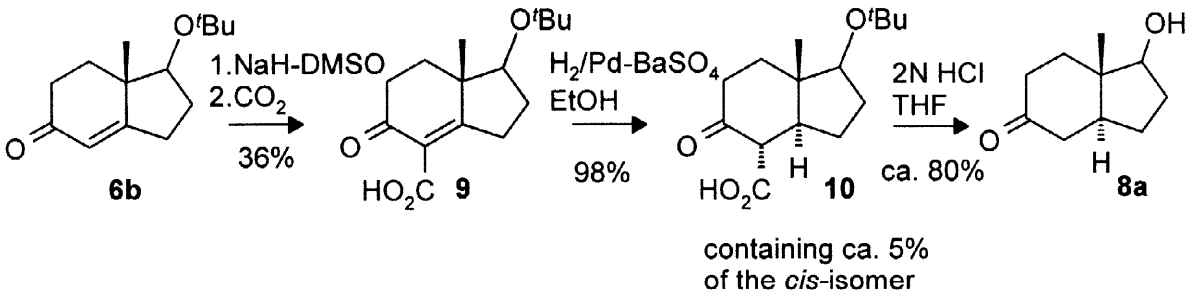
a. R^1= H, R^2=OH, R^3=H
b. R^1= H, R^2=O^{t}Bu, R^3=H
c. R^1= $(CH_2)_2C_6H_4$-*m*-OMe, R^2=OH, R^3=H
d. R^1= $(CH_2)_2CO_2H$, R^2=OH, R^3=H
e. R^1= CO_2Et, R^2 and R^3=O

Table 2.

		Catalyst/solvent	Product, yield(%) *cis*	*trans*	Ref.
1	**6a**	5%Pd-C/ethanol	**82**		17
2	**6b**	5%Pd-C/*n*-hexane	**62.5**	**27.5**	17
3	**6c**	10%Pd-C/ethanol	--	**100**	18
4	**6d**	10%Pd-C/ethanol	--	**60**	19
5	**6e**	Pd-C/ethanol	--	**64**	19

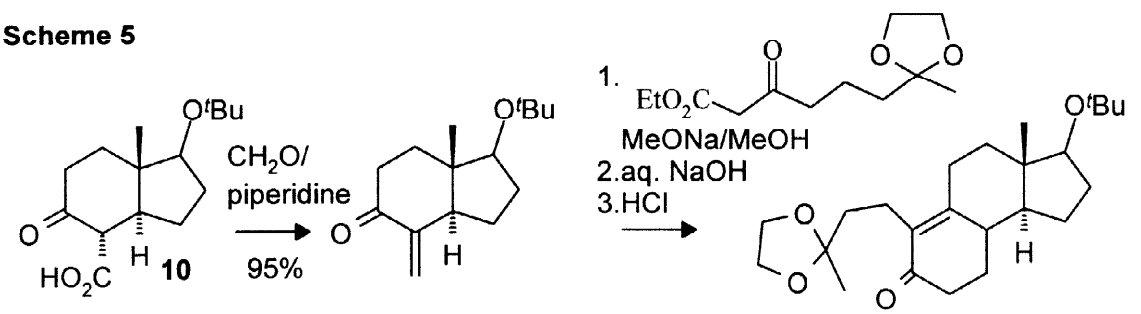
[1]The only product

Scheme 4



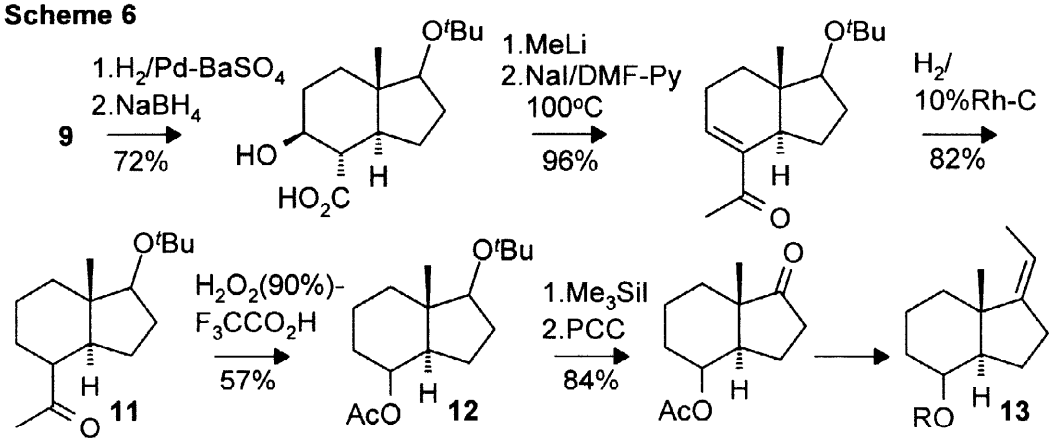
On the grounds of the above results, enone **6b** was transformed[17] into its 14α-dihydro derivative **8a** in four steps (Scheme 4). Carbonylation of **6b** gave keto acid **9** in 36% yield (some unchanged starting material was recovered). Hydrogenation of **9** afforded the *trans*-fused product **10** with the equatorial (α) carboxy group, contaminated with the *cis* isomer (ca. 5%). Hydrolysis and decarboxylation of **10** gave the final product **8a**. An example[20] of an early application of compound **10** in the steroid total synthesis is outlined in Scheme 5.

Scheme 5



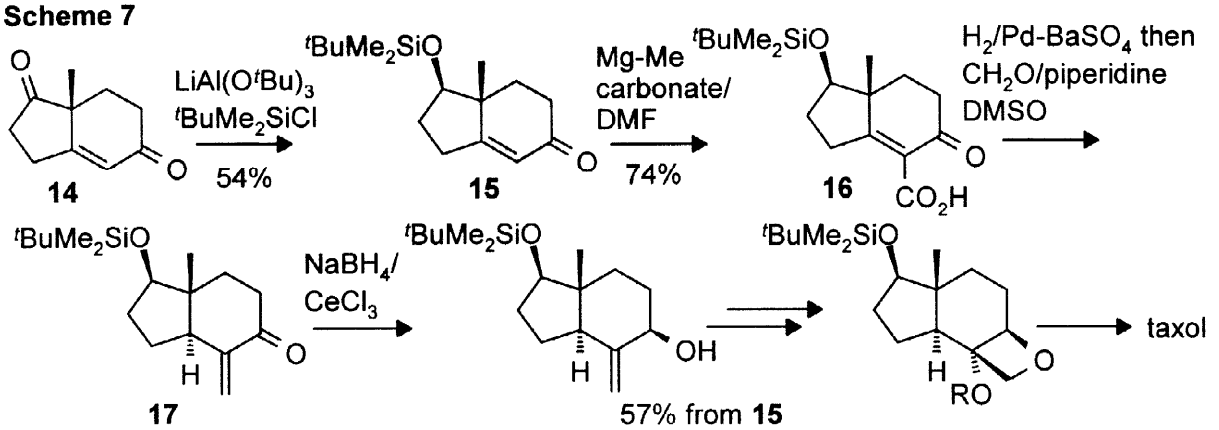
Transformation of keto acid **9** into the vitamin D building block **13** is presented in Scheme 6.[21,22] The scheme is self-explanatory; the relatively harsh conditions of the Baeyer–Viliger reaction (**11**→**12**) should be noted.

Scheme 6



A recent application of catalytic hydrogenation for the construction of a *trans*-fused hydrindane system by Danishefsky and co-workers[23] is presented in Scheme 7. Regioselective reduction of the carbonyl group in the five-membered ring in the Hajos–Parrish–Wiechert ketone (**14**) (for preparation and comments, see, section 2.3) was achieved with tri-(*tert*-butoxy)lithiumaluminum hydride. After protection of the hydroxy group, unsaturated ketone **15** was carboxylated to yield **16**. The latter was hydrogenated and then hydroxymethylated. The intermediate underwent decarboxylation and dehydration to afford *trans*-fused **17**, which was further used in taxol synthesis.

Scheme 7



Craig and coworkers have reported [24,25] that the disubstituted double bond in **18** (Scheme 8) is saturated under condition of catalytic hydrogenation to give **19** which resisted any further changes.

Scheme 8

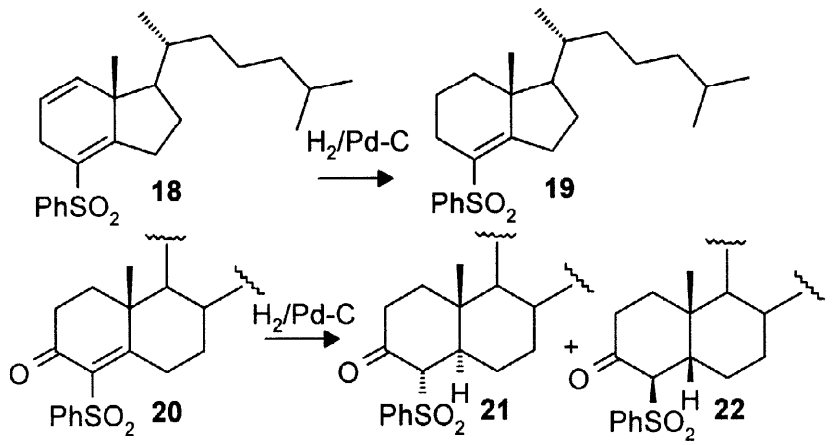


Table 3.

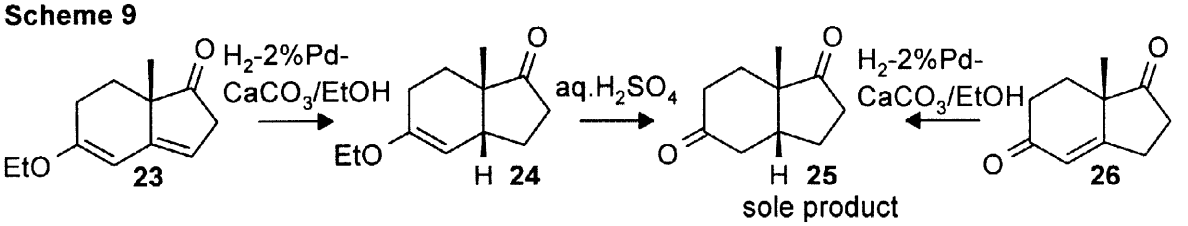
solvent	temp.	time	conversion %	**21** : **22** ratio
EtOH (95%)	reflux	5h	100	6.5 : 1
AcOEt	r. t.	20h	100	5.0 : 1
AcOEt[a]	r. t.	4h	100	2.5 : 1
hexane[b]	r. t	7 days	20	> 10 : 1

[a] added four equivalents of CF_3CO_2H; [b] reaction was carried out in a suspension

In our laboratory[26] model studies on catalytic hydrogenation of phenyl sulphonyl cholestenone **20**[27] were carried out. It has been found that the reaction in EtOH at room temperature was slow. However, at the reflux temperature it afforded a mixture of *trans* and *cis* products **21** and **22** respectively, the former predominating, as indicated in Scheme 8 and Table 3. The reaction was somewhat faster in AcOEt at room temperature, affording a smaller amount of the *trans* product. Addition of triflouroacetic acid considerably enhanced the reaction rate, but decreased

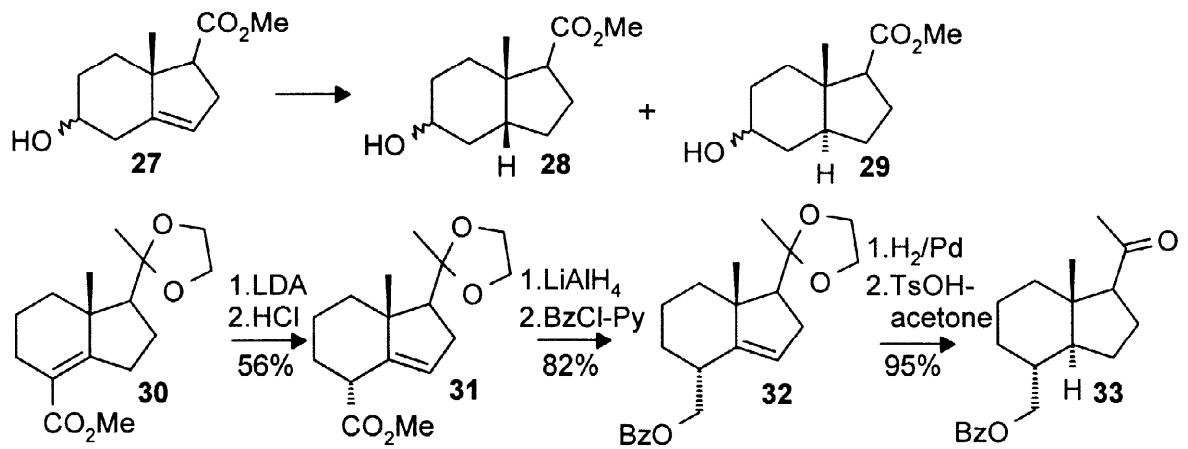
its selectivity. When **20**, as a suspension in hexane, was hydrogenated at room temperature only the *trans* product was formed, although after 7 days only 20% of starting material was consumed. In some other cases the reaction was complicated by formation of the enolate of **20** which gave a mixture of products on catalytic hydrogenation.

Scheme 9



Reduction of enol ethers derived from hydrindane enones also affords the respective 5β products.[15] Thus, ketone **26** and its enol ether **23** afford the same diketone **25** on catalytic hydrogenation (and hydrolysis in the latter case) (Scheme 9).

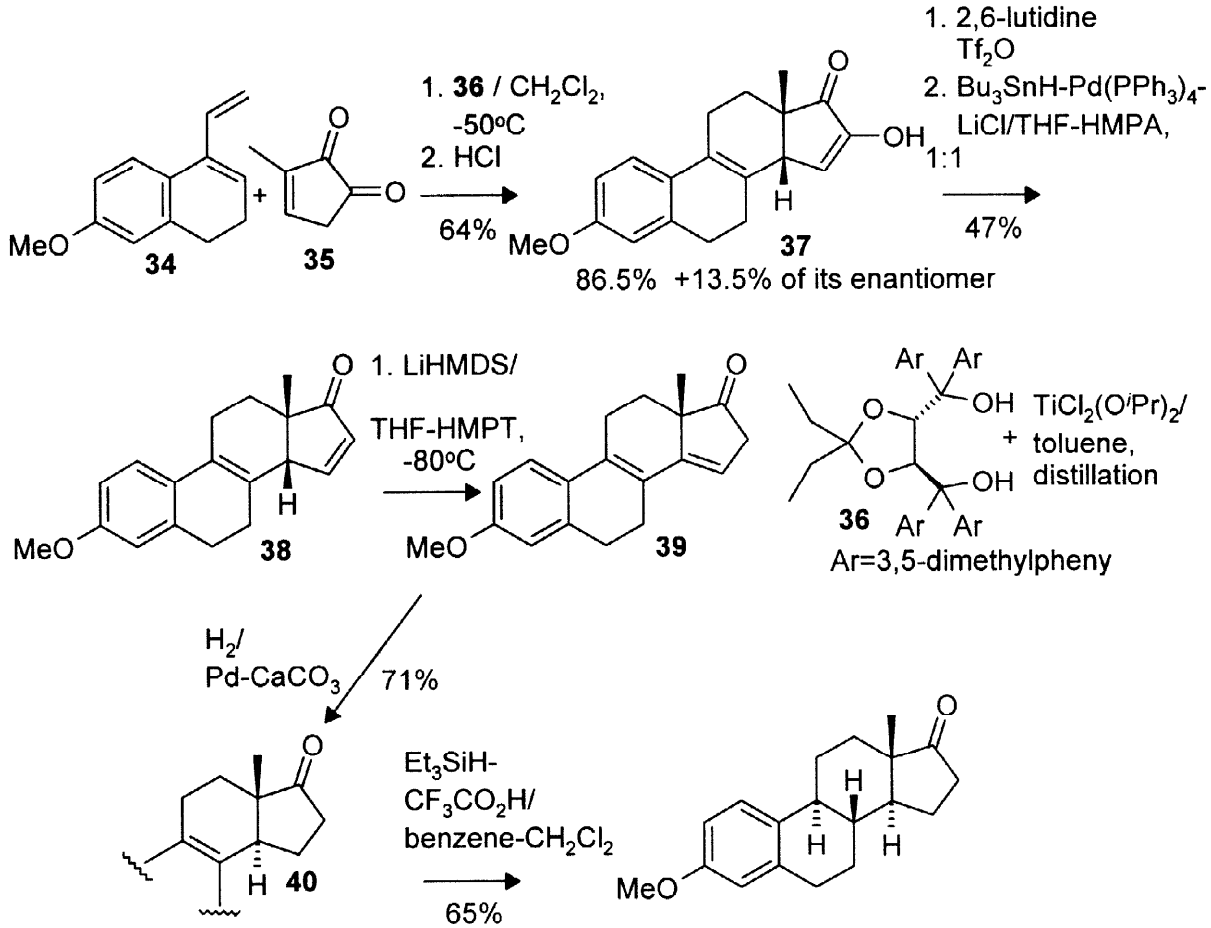
Scheme 10



Heteroannular homoallylic alcohol **27** (Scheme 10) was reported[28] to give the product of hydrogen addition on the α-side predominantly (*cis:trans* = 1:1.8) on catalytic hydrogenation. This result was questioned by other researchers who obtained only *cis*-hydrindanes on reduction of a similar mixture of alcohols.[29] On the other hand, Mandai *et al.*[30] have reported that catalytic hydrogenation of 14,15-ene **32** afforded exclusively *trans*-product **33** (Scheme 10). The intermediate **32** was prepared from 8(14)-ene **30** by deconjugation (LDA and then HCl) which provided the 8α-carbomethoxy derivative **31** (56%) along with its 8β isomer (5%), and unchanged starting material **30** (37%). Ester **31** was then reduced with $LiAlH_4$ and the resulting alcohol was benzylated. Catalytic hydrogenation of 8(14)-intermediate **30** was not mentioned.

Quinkert and coworkers[31,32] have developed the synthesis of the estrane derivative **39**, utilizing Dane's[33-35] diene **34** (Scheme 11). The Diels–Alder reaction of **34** and **35** catalysed by Ti-TADDOL-ate **36**[36] afforded the adduct (64% yield) consisting of 86.5% **37** and 13.5% of its enantiomer. Reduction of **37** followed by crystallization gave the pure product **38** in 47% yield. Deconjugation of the α,β-unsaturated ketone **38** provided the optically active Torgov's estrapentaene [37] **39**, which was hydrogenated over palladium catalyst to generate *trans*-hydrindane rings system[38] **40**. The intermediate **40** (Scheme 11) was treated with Et_3SiH and CF_3CO_2H to affect saturation of the tetra-substituted double bond.[39,40] Quinkert's natural estrone (methyl ether) synthesis comprises ten steps and affords the product in ca. 15% overall yield from the diene **34**.[41]

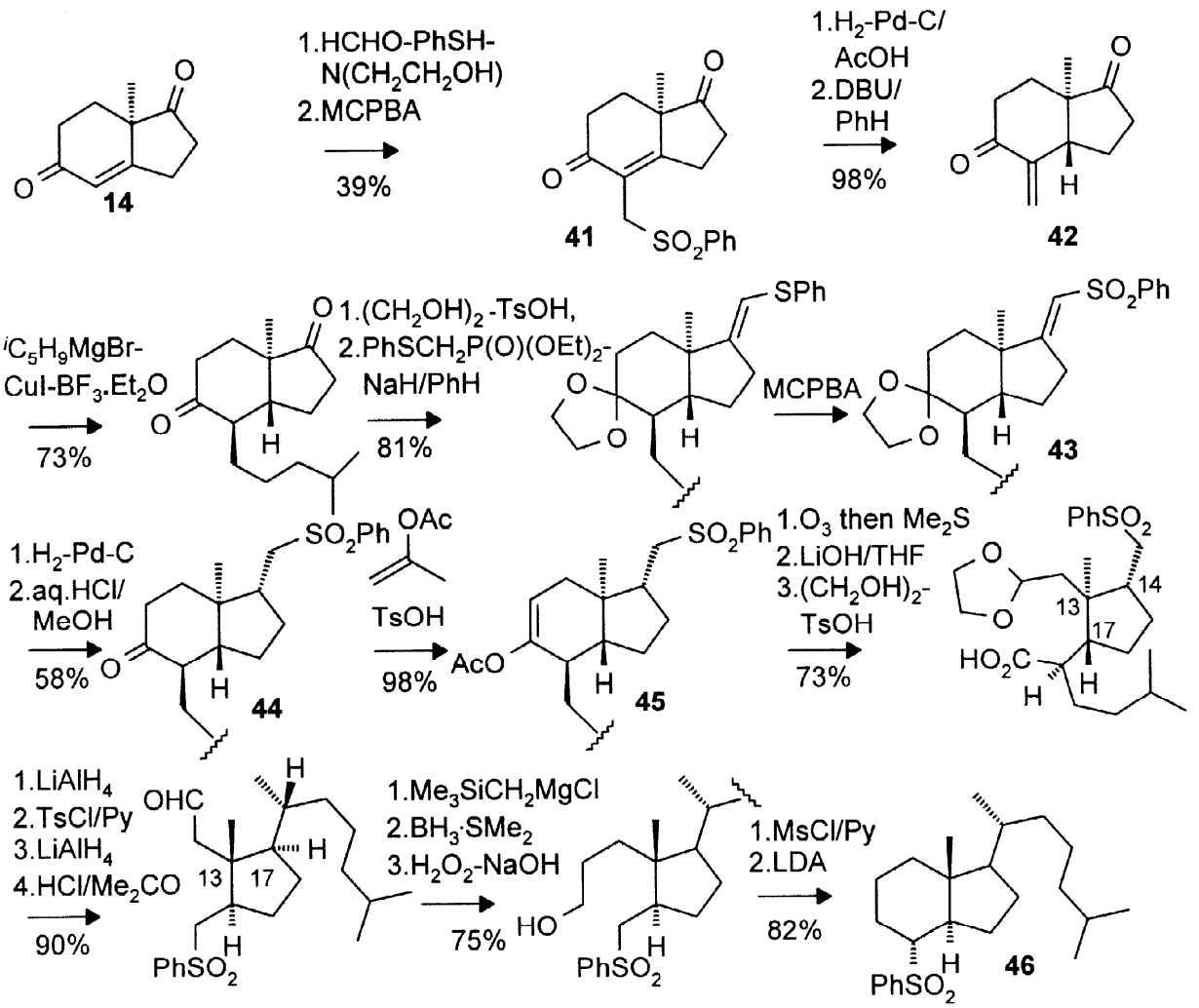
Scheme 11



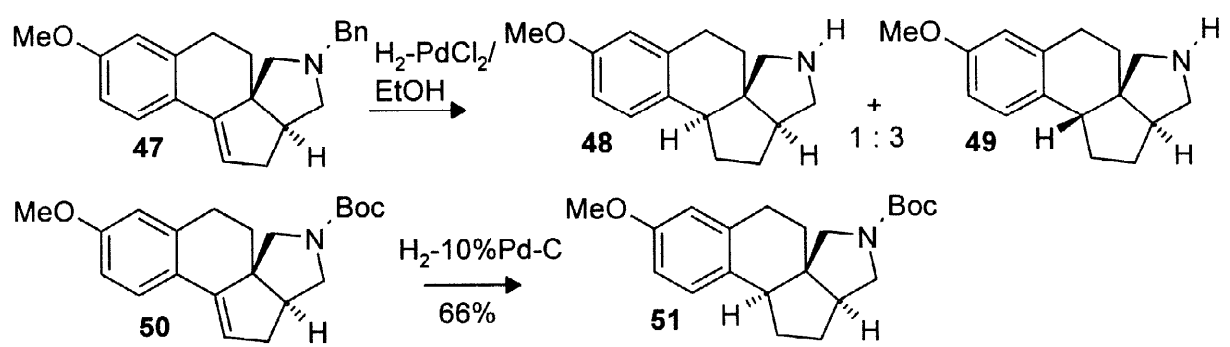
In the synthesis of sulfone **46**[42-44] by Kametani and co-workers, (-)-dione **14** (Scheme 12) was used as an easily accessible optically active starting material. Stereoselective catalytic hydrogenation of a double bond was applied twice in the course of a complex multi-step transformation. Hydrogenation of **41**, followed by phenyl sulfonyl group elimination, yielded *trans*-hydrindane derivative **42**. In this reaction a chiral centre at the latent C_{17} was generated. Hydrogenation of vinyl sulfone **43** occurred on the opposite site to the angular methyl group to provide **44** introducing the third chiral centre into the five-membered ring (latent C_{14}). Stereochemistry of this reaction was crucial for the foresaw opening of the six-membered ring in **45** and regenerating a *trans*-hydrindane system. The synthesis embraces over 20 steps and affords the final product in ca. 5% yield.

Meyers and co workers[45] have applied catalytic hydrogenation in the total synthesis of conessine. Addition of hydrogen to the *N*-benzyl derivative **47** (Scheme 13) afforded debenzylated and saturated product as a mixture of *trans-cis* isomers, **48** and **49**, with the latter (undesired) prevailing (1:3). It was reasoned that hydrogenolysis of the *N*-benzyl group occurred before the double bond hydrogenation and that the deprotected amine function was responsible for hydrogen addition from the β-face of the molecule. Indeed, hydrogenation of the related carbamate **50** (*N*-Boc) proceeded with hydrogen delivery from the α-side yielding exclusively the *trans* product **51** .

Scheme 12

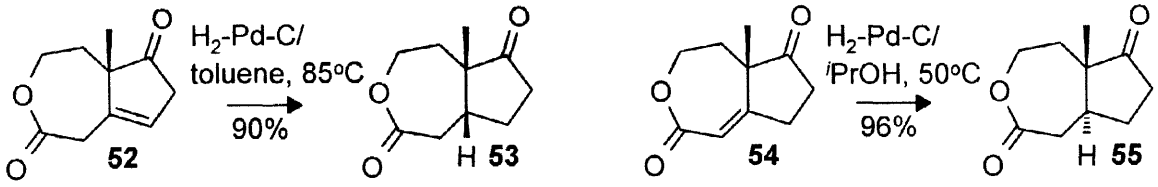


Scheme 13



An interesting case of different stereochemical outcome of hydrogenation of quite similar hydrindane derivatives was reported by Daniewski and Kiegiel.[46] While compound **52** (Scheme 14), with the double bond in the five-membered ring, afforded *cis*-fused product **53**, its isomer with the double bond in the seven-membered ring **54** gave selectively *trans*-fused product **55**, which was used for estrone synthesis.

Scheme 14



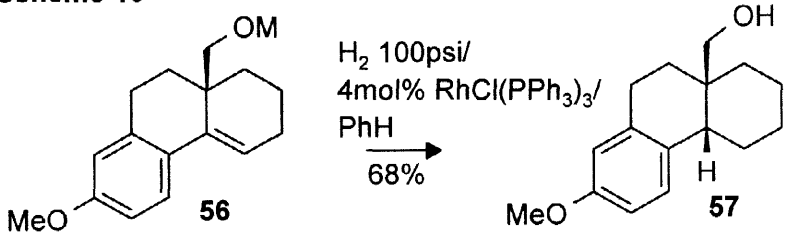
Hydrogenation of cholest-4-en-3-one over palladium catalyst with benzyl alcohol serving as the hydrogen donor was reported.[47] Its stereochemical outcome did not differ from the classic hydrogenation.

2.2. Homogeneous catalytic hydrogenation

Hydrogenation of steroids and similar compounds with the use of homogeneous catalysts is much less known than the corresponding heterogeneous processes.[48-50] Djerassi and Gutzwiller[51] have found that hydrogenation of cholest-4-en-3-one in the presence of the Wilkinson catalyst ($ClRh(PPh_3)_3$) resulted in only 20% of the saturated product after 70 h (no stereochemical assignment was made). This catalyst proved, however, useful in preparation of deuterium-labelled compounds.[52] It has been shown that catalytic deuteration of testosterone affords the product with *trans*-fused AB rings only, which suggested that homogeneous catalysts have a different stereochemical profile than heterogeneous ones (although the cholesterol double bond hydrogenation with the Wilkinson catalyst [53] afforded 5α-H product only, in the same way as with the use of Pd-on-carbon or PtO_2).

Nishimura and coauthors[54] performed hydrogenation of androst-4-en-3,17-dione with ruthenium complexes, $RuCl_2(p\text{-}xC_6H_4)P)_3$, where X=H or OMe, in benzene. A mixture of dihydro-derivatives was obtained, the composition of which was not determined.

Scheme 15



M= K, Na or Li

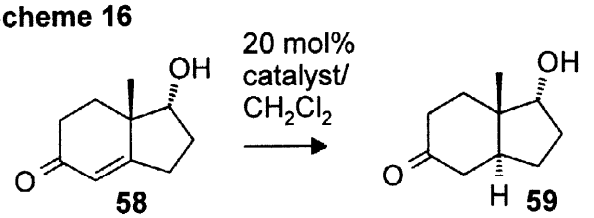
A directing effect related to the hydroxy group was observed on hydrogenation of the phenanthrene derivative **56** (Scheme 15) using the Wilkinson catalyst.[55] The hydrogen atoms were added exclusively from the side of the hydroxyl group to give the *cis* decaline derivative **57**. The same compound (**56**) upon hydrogenation over a heterogeneous palladium catalyst under different conditions was transformed into mixtures of products containing considerable quantities of the *trans* isomer (see Scheme 2 and the comment). This suggests that the homogeneous catalyst potentiates the hydroxy group directing effect.

In the absence of directing groups, a bias of homogeneous catalysts for α-face hydrogenation of steroid 4-en-3-ones was confirmed with an iridium-based catalyst.[56] For example, androst-4-en-3,17-dione was hydrogenated with (Ir(cod)(tricyclohexylphosphine)(py))PF_6 (the Crabtree catalyst[57,58]) to afford the *trans* derivative in 70% yield. The iridium complex makes possible fast hydrogenation of relatively hindered double bonds; for example, O-*tert*-butyldimethylsilyl cholesterol was hydrogenated during 1 h to give the corresponding *trans* product only. However, polar groups (especially the hydroxy group) deactivate the catalyst.

A detailed study of the hydrogenation of androst-4-en-3,17-dione, 17α-methyltestosterone and cholest-4-en-3-

one with the use of *in situ* prepared phosphine rhodium catalysts was reported.[12] It was found that the activity and selectivity of catalysts markedly depends upon the solvent and ligand properties. The catalysts prepared from $ClRh(PPh_3)_3$ and low basicity phosphines promote the formation of *trans* products. The best results were obtained with norbornadiene rhodium(I) chloride dimer $(Rh(NBD)Cl)_2$ and $MePh_2P$ in a mixture of *iso*-PrOH-benzene, 4:1, at 70 °C. Under these conditions androst-4-en-3-one afforded the *cis:trans* products in a ratio of 1:9.

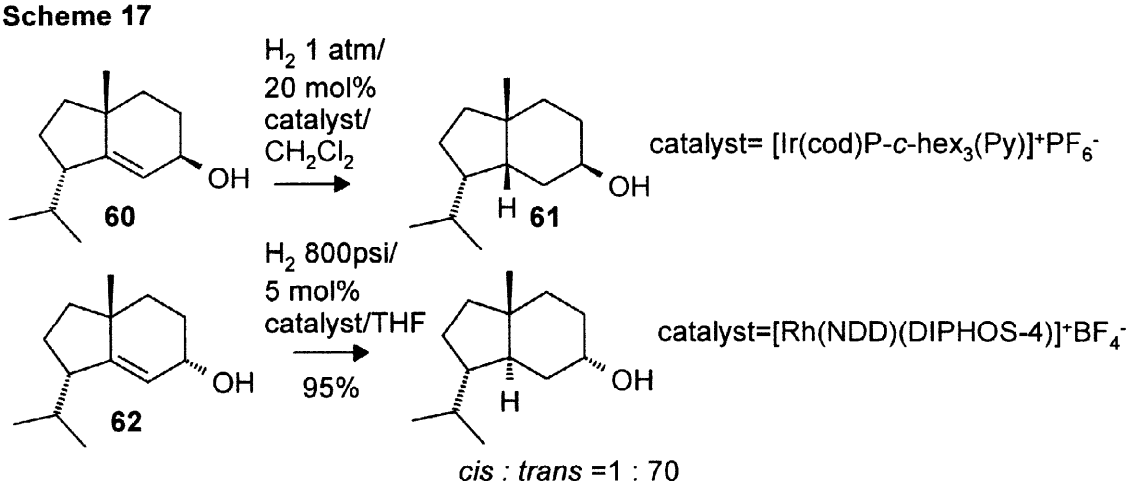
Scheme 16



catalyst=$[Ir(cod)py(PCy_3)]^+PF_6^-$ *cis/trans* = 4:96

Stork and Kahne[59] have examined hydrogenation of some hydrindane derivatives with the Crabtree catalyst. These authors have found that the derivative **58** with the 17α-hydroxy group is smoothly hydrogenated and affords exclusively the *trans*-product **59** (Scheme 16), but compounds lacking the 17α-hydroxy group yield mixtures of *cis* and *trans*-products in proportions similar to those obtained from hydrogenation over a heterogeneous catalyst.

Scheme 17

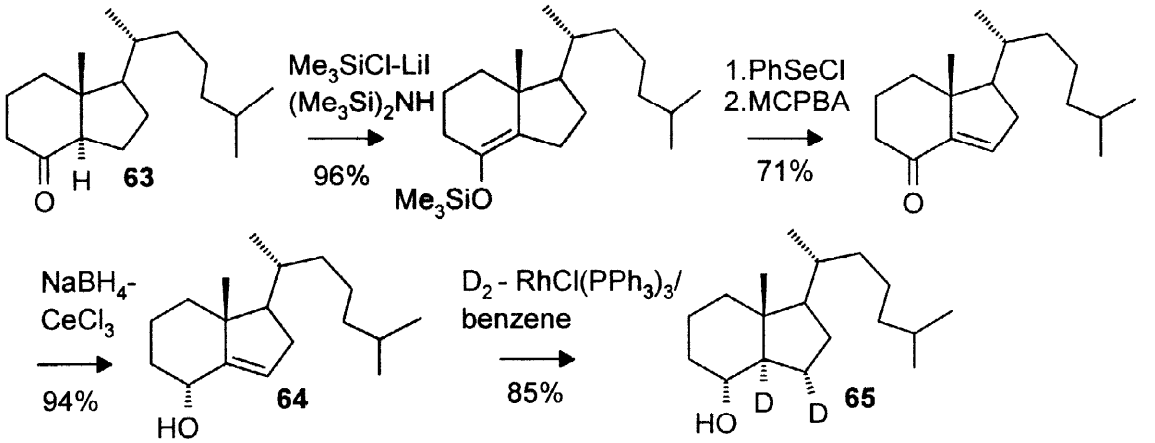


cis : *trans* =1 : 70

Allylic alcohol **60** was prepared almost quantitatively by $LiAlH_4$ reduction of the corresponding ketone. The hydroxy group configuration of **60** was assigned on the basis of its strong directing effect resulting in the production of the *cis*-hidrindane **61** on hydrogenation with the Crabtree catalyst.[60] Compound **62** with α-oriented hydroxy group was hydrogenated over a rhodium catalyst[61] at 800 psi (Scheme 17) to produce a mixture of saturated products with *cis*:*trans* ratio of 1:70. It should be noted that in the case of **62** steric congestion of the highest order was overridden by the hydroxy group directing effect (cf. Schemes 40 and 48).

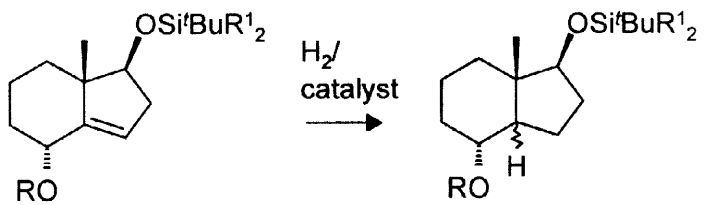
The Wilkinson catalyst was applied for deuteration of the 14,15-double bond in the derivative hydrindane **64** (Scheme 18) in the course of *cis*-isotachysterol synthesis. Hoeger and Okamura[62] have found that **64** afforded *trans*-(**65**) and *cis*-products in a ratio of 37:1 and pointed out that catalytic hydrogenation may be useful for generating the *trans*-hydrindane system.

Scheme 18



A comparison of the selectivity of hydrogenation with the Crabtree and Wilkinson catalysts has been carried out by the Spanish authors[63] using four hydrindane derivatives (Scheme 19, Table 4). With the Crabtree catalyst a complete β-selectivity of hydrogen addition was observed for the free alcohol and acetate, irrespective of the function at C_{17} (Table 4, entries 1,2 and 4). The methoxymethyl derivative resisted hydrogenation (entry 3). The rhodium catalyst afforded predominantly *trans*-fused product. However, acceptable yields were obtained only for free alcohols and the selectivity was rather disappointing (entries 1 and 4).

Scheme 19



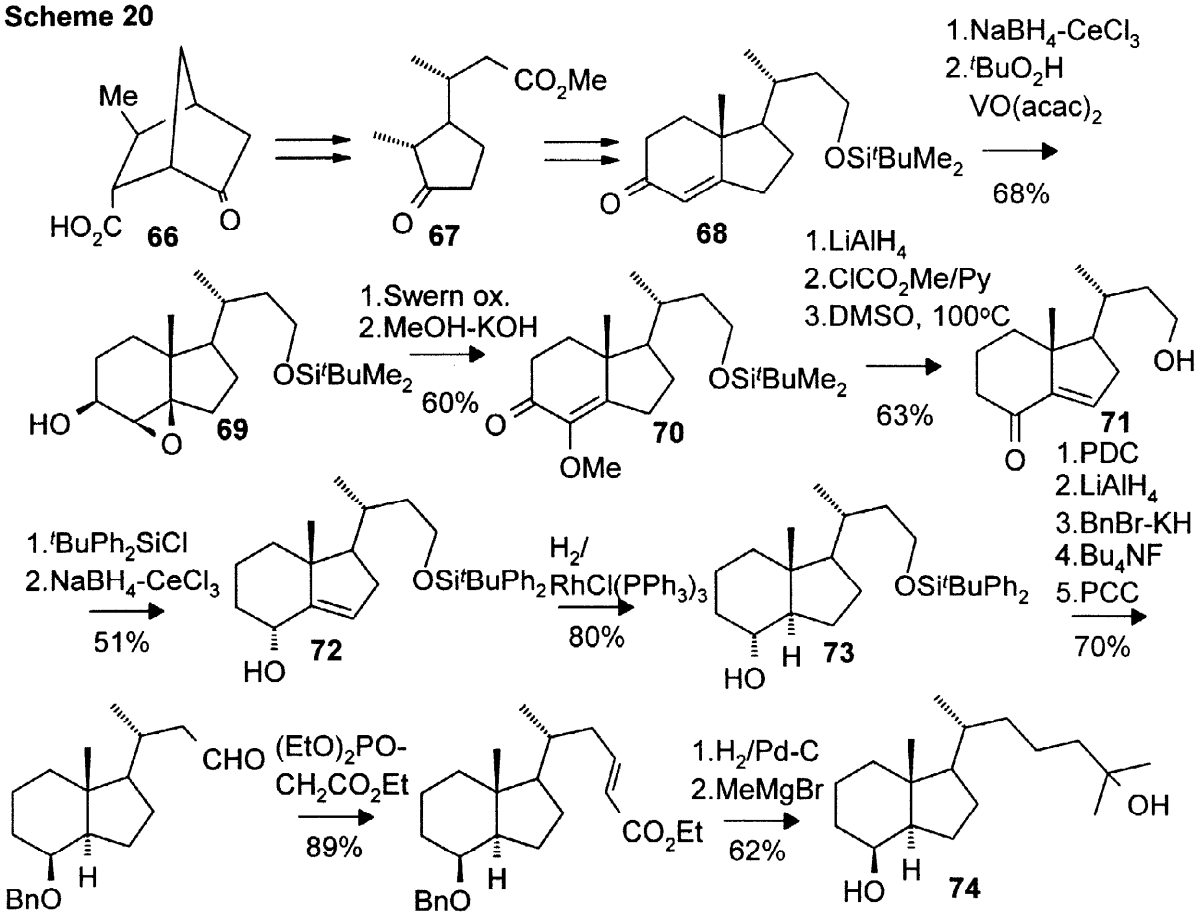
Catalysts:
$[Ir(Cod)Py(PCy)_3]PF_6$ in CH_2Cl_2 (Crabtree)
$RhCl(PPh_3)_3$ in PhH (Wilkinson)

Table 4.

	R	R^1	Catalyst	cis:trans	Yield (%)
1	H	Me	Crabtree	100:0	92
			Wilkinson	25:75	87
2	Ac	Me	Crabtree	100:0	78
			Wilkinson		-
3	MOM	Me	Crabtree		-
			Wilkinson		-
4	H	Ph	Crabtree	100:0	87
			Wilkinson	35:65	87

The double bond hydrogenation has been an important step in vitamin D synthesis as outlined in Scheme 20.[64,65] Easily available optically active norbornane derivative **66**[66,67] was transformed diastereoselectively (with reductive C-C bond cleavage as the key step) into cyclopentanone **67** and then into the hydrindane **68**. Reduction of the double bond and transposition of the oxygen function in this intermediate was achieved in the following way. Reduction of the keto group, followed by epoxidation of the double bond[68] afforded **69**. It is noteworthy that α,β-unsaturated ketone **68** could not be epoxidized with alkaline hydrogen peroxide in contrast to a model decalin system. Re-oxidation of the hydroxy group in **69** and treatment of the intermediate ketone with methanolic KOH gave **70**. Reduction of the keto group and then esterification of the resulting alcohol with ethyl chloroformate, followed by the carbonate pyrolysis, yielded **71**. Stereoselective reduction of the carbonyl group afforded allylic alcohol **72**, which was then subjected to hydrogenation with the Wilkinson catalyst. The hydrogen addition occurred exclusively on the side of the hydroxyl group. The intermediate **73** was transformed into the final product **74**, as shown in the scheme. The entire synthesis involves 26 steps and affords the product in ca. 1.5% yield.

Scheme 20

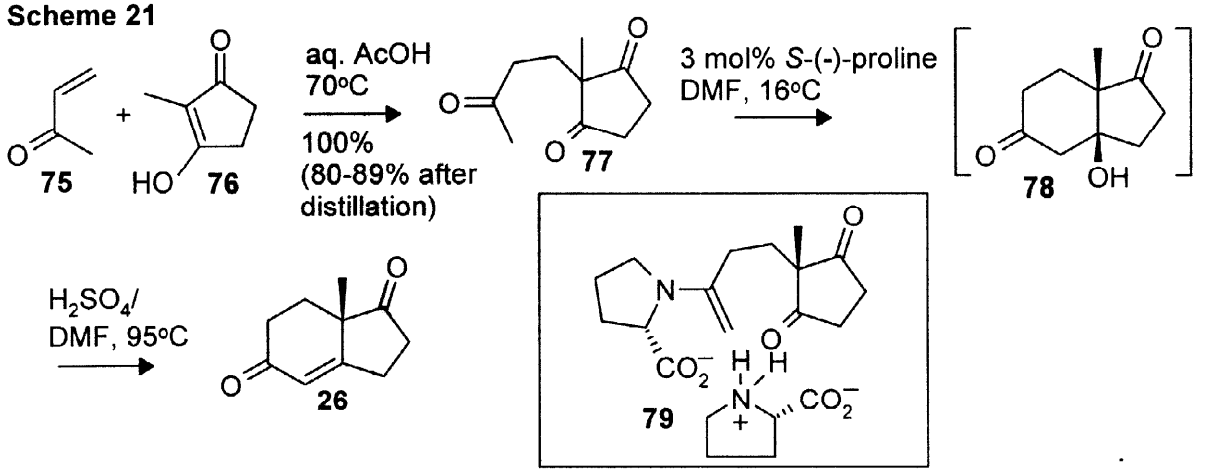


2.3. Comments on synthesis of Hajos–Parrish–Wiechert ketone

The discovery of an economic enantioselective route to endione **26** had a great impact on steroid total synthesis and on synthetic methodology in general. Some comments regarding this pivotal compound are in order. Endione **26** was first prepared in racemic form by Wieland and Miescher.[69] Optically active **26** was obtained by Prelog and coworkers[70] using a microbiological reduction of the racemate. A method for the enantioselective synthesis of **26** was developed by Hajos and Parrish[20,71,72] at the Hoffmann La Roche (Nutley, USA) and,

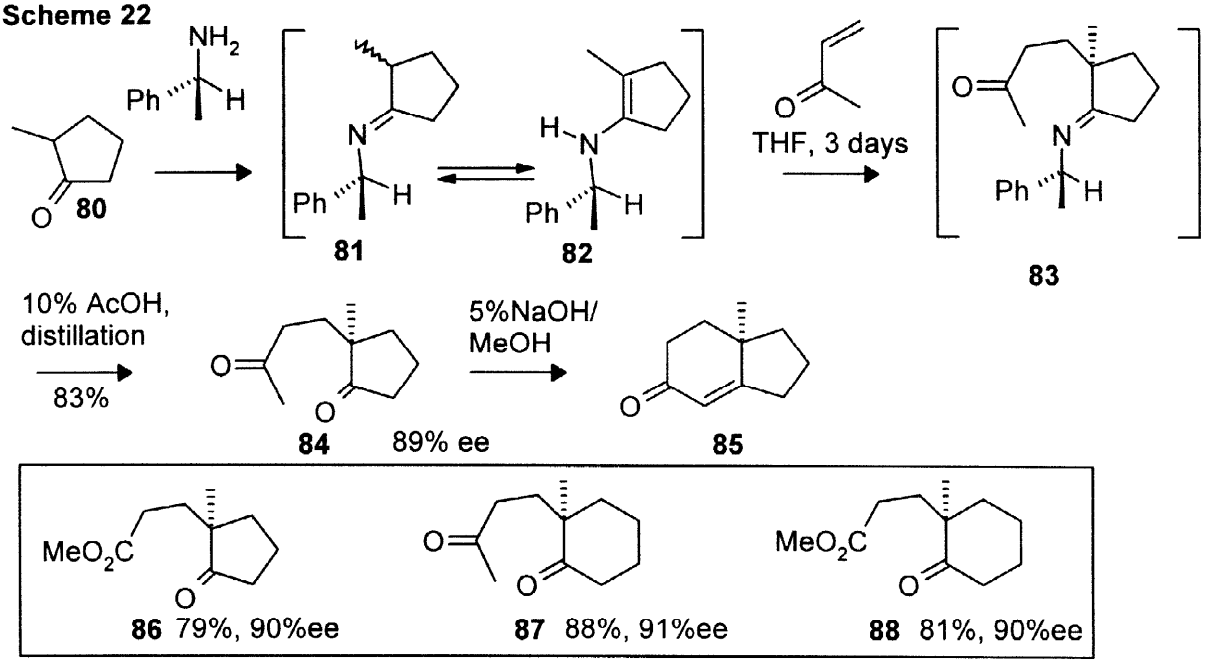
independently, by Wiechert and his coworkers.[73] at the Schering (Berlin). The American authors[74] recommended acid catalysed conjugated addition of methyl vinyl ketone **75** and 2-methylcyclopenta-1,3-dione **76** (Scheme 21), which afforded triketone **77** in virtually quantitative yield (80-89% after distillation). Then (*S*)-(–)-proline catalysed cyclization of **77** in DMF gave ketol **78**, which was dehydrated with H_2SO_4 in DMF, without isolation, to yield endione **26** (70-76% yield, 99-99.4% ee). In the alternative approach triketone **77** was treated simultaneously with proline and 1N $HClO_4$ in refluxing acetonitrile to affect simultaneous cyclization and dehydration,leading directly to **26** .

Scheme 21



The scope and mechanism of this enantioselective aldol reaction has received considerable attention.[75] It has been postulated that enamine is formed by the methyl ketone carbonyl group and proline,[76] whereas the second proline molecule is involved in complexation during cyclization[77,78](the intermediate structure **79** is shown in Scheme 21).

Scheme 22



A different general approach to the enantioselective synthesis of hydrindanone derivatives has been offered by the French workers.[79] 2-Methylcyclopentanone **80** (Scheme 22) was treated with commercial (*S*)-(–)-1-

phenylethylamine and a catalytic amount of *p*-TsOH (in toluene at reflux temperature with azeotropic removal of water) to form the enamine as a mixture of tautomers **81** and **82**. The reaction of the enamines with methyl vinyl ketone (MVK) afforded a Michael adduct **83**, which was hydrolyzed with aqueous acetic acid without isolation. (*R*)-Diketone **84** was obtained in 83% yield from enamine **81** and the starting amine was regenerated quantitatively without any loss of optical purity. Optical purity of product **84** was determined to be 89%. It is noteworthy that alkylation of enamine **81** occurred regioselectively at the more substituted position.[80] The usual cyclization of **84** afforded hydrindane derivative **85**. Likewise, the reaction of enamine **81** with methyl acrylate gave keto ester **86** with high optical purity. The enamine generated from 2-methylcyclohexanone and (*S*)-(–)-1-phenylethylamine afforded diketone **87** and keto ester **88** in reactions with MVK and methyl acrylate, respectively. It has been shown recently that Michael-type alkylation of chiral imines may be successfully applied to 2-methylcycloheptanone and 2-methylcyclooctanone.[81]

3. Metal hydride reduction of an activated C-C double bond at rings junction and related reactions

3.1. Iron hydrides

Reduction of α,β-unsaturated carbonyl compounds, including some steroids with a complex iron hydride, $NaHFe_2(CO)_8$ in THF containing AcOH has been studied by Colleman and coworkers.[82] It was found that testosterone afforded the dihydro product as a mixture of *cis:trans* isomers in a ratio of 10:1 (10% yield). Under similar conditions the decalin related enone **106** (Table 5) gave *cis:trans* products in a ratio of 7:1 (99% yield).

A complex iron hydride, prepared from $Fe(CO)_5$ and a small amount of NaOH in the two-phase ether-water system was used for the reduction of conjugate carbonyl compounds by Noyori and coworkers.[83] This reagent transformed cholest-4-en-3-one into 5β-cholestanone (exclusive product, 32% yield) and **106** into saturated derivatives, *cis/trans* ca. 2:3, 35% yield.

3.2. Silanes

$TiCl_4$ - catalysed hydrosilylation of cholest-4-en-3-one with Me_3SiH afforded 5β/5α cholestanes in a ratio of 3:1 (81% yield).[84] Compound **106** gave the corresponding isomers, 9:1, 53% yield.

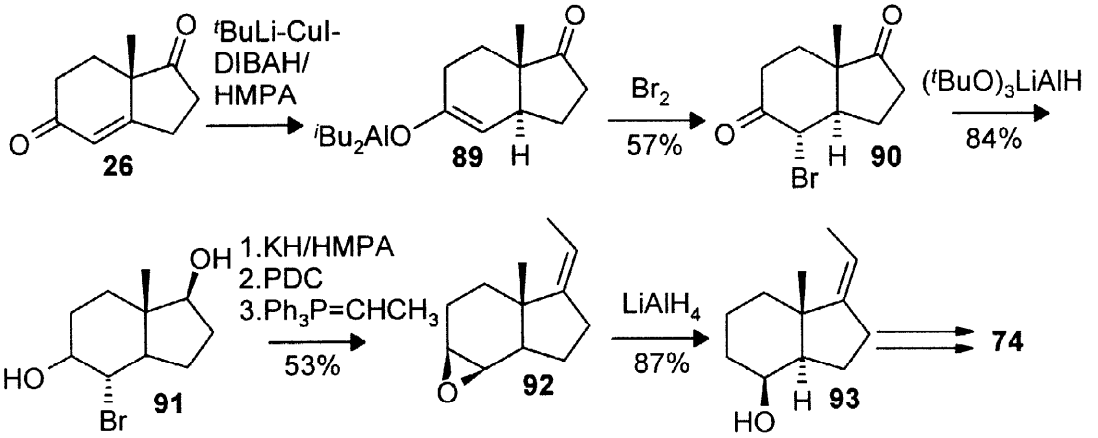
Extensive studies on the hydrosilylation of α,β-unsaturated carbonyl compounds performed by Kainan and Greenspoon[85] included some steroid substrates. The best results as far as yields are concerned were obtained using diphenylsilane with $Pd(PPh_3)_4$ and $ZnCl_2$ as co-catalysts. The reaction of these reagents with cholest-4-en-3-one favoured the *trans* isomer (*cis:trans* 2:3, 68% yield). This tendency was confirmed by other authors[86] who performed hydrosilylation of hydrindane derivative **99** (Table 5) and obtained the *cis:trans* products in a ratio of 42:58 (58% yield together with some starting material). However, the stereoselectivity was too low to secure application of this technique in multi-step syntheses.

3.3. Copper hydrides

Research on the application of copper hydride for conjugate addition of the hydride anion to α,β-unsaturated carbonyl compounds followed shortly after Corey[87] and Posner[88,89] with their respective coworkers had developed organocuprate reagents for the alkyl transfer. Boeckman[90] has shown that the complex generated from CuH[91] and pentyl lithium in THF-HMPA affects clean reduction of a conjugate double bond. Decalin derivatives afforded mixtures of *cis/trans* isomers with the former predominating. A hydrindane derivative was also investigated. Some results are compiled in Table 5. Complex copper hydride, LiCuH(n-butyl) prepared from CuH and *n*-BuLi, also affected reduction of enone **106** (entry 3). Interestingly, addition of HMPA was not necessary.[92]

Tsuda, Saegusa and their coworkers[93,94] have discovered that a catalytic amount of MeCu, generated *in situ* from MeLi and CuI, has a dramatic effect on the properties of DIBAH.[95] Reduction of α,β-unsaturated steroid ketones with the MeLi-CuI-DIBAH reagent in a mixture of THF and HMPA at -50 °C gave saturated ketones with a *trans* junction of the A/B rings. Likewise, reduction of hydrindane-related enone **107** (Table 5) yielded a mixture of *cis*- and *trans*- fused products in a ratio of 12:88 (Table 5, entry 4). It has been assumed that the reagent involves CuH.

Scheme 23



Selectivity of the reduction with alkylcopper-DIBAH system was investigated by A. R. Daniewski and coworkers.[96] These authors have recommended the use of *t*-BuLi or *t*-BuMgCl instead of MeLi. Examples of the results obtained by the authors with this reagent are presented in Table 5 (entry 5) and Scheme 23. The Daniewski's modification has been successfully applied by some other research groups.[97] More recently, Australian researchers[86] (see also Scheme 24) attained a similarly high selectivity with the reagent prepared from MeLi or BuLi (entries 6 and 7). An important new modification introduced by those researchers consists in the use of CuCN as the copper source (instead of CuI). It is noteworthy that HMPA was not a necessary component of the reaction mixture, presumably because the phosphine oxide moiety, present in the starting material, acts as the CuH ligand. Examples of applications of CuH reduction to the vitamin D synthesis are presented in Schemes 23 and 24. In the approach by A. R. Daniewski and Kiegiel (Scheme 23) the Hajos–Parrish–Wiechert ketone (**26**) was treated with complex copper hydride and then the product, supposedly the aluminium enolate **89**, was quenched with bromine to give bromo dione **90** (with a *trans* ring junction). Reduction of the keto groups in **90** afforded diol **91** which was subsequently treated with KH in HMPA to yield 8β,9β-epoxide. Oxidation of epoxy alcohol with PDC afforded the epoxy ketone which was reacted with ethyltriphenylphosphonium iodide and *t*-BuOK in THF to give **92**. Finally, the treatment of **92** with $LiAlH_4$ in THF at reflux temperature provided the key intermediate **93** (cf. Scheme 6) in a remarkably high overall yield, 22%.

A concise synthesis of vitamin D compounds was reported by Haynes and coworkers[98,86] (Scheme 24). To a solution of anion generated from **94**,[99] methylcyclopentenone **95** and methyl vinyl ketone derivative **96** were consecutively added to give compound **97** in 53% yield. Diene **97** was hydrogenated over a palladium catalyst in AcOEt (with some pyridine added to prevent epimerisation at C_{20}) and the product **98** was subjected to annulation. α,β-Unsaturated ketone **99** was reduced with the MeCu-DIBAH reagent and the resulting enolate was quenched with Br_2. Bromoketone **100** was obtained, the reduction of which yielded a mixture of alcohols **101** with the α:β isomer ratio of 83:17. The mixture of alcohols was subjected to the epoxide forming reaction and then, the product **102** was

treated with DIBAH. Chromatography of the resulting mixture afforded the required 8-hydroxy derivative **103** and unreacted 9α-hydroxy-8α-bromide **101**. The key intermediate **103** (racemic) was obtained in seven steps from allylic phosphine oxide, in overall yield of 18%. In the subsequent steps, dianion generated from **103** and butyllithium was treated with an excess of methacrolein to give an adduct (80% yield) which was then treated with NaH in DMF to give unstable diene **104** as a mixture of (*E*)- and (*Z*)-isomers. The mixture **104** was subjected to catalytic hydrogenation to give **105**.

Scheme 24

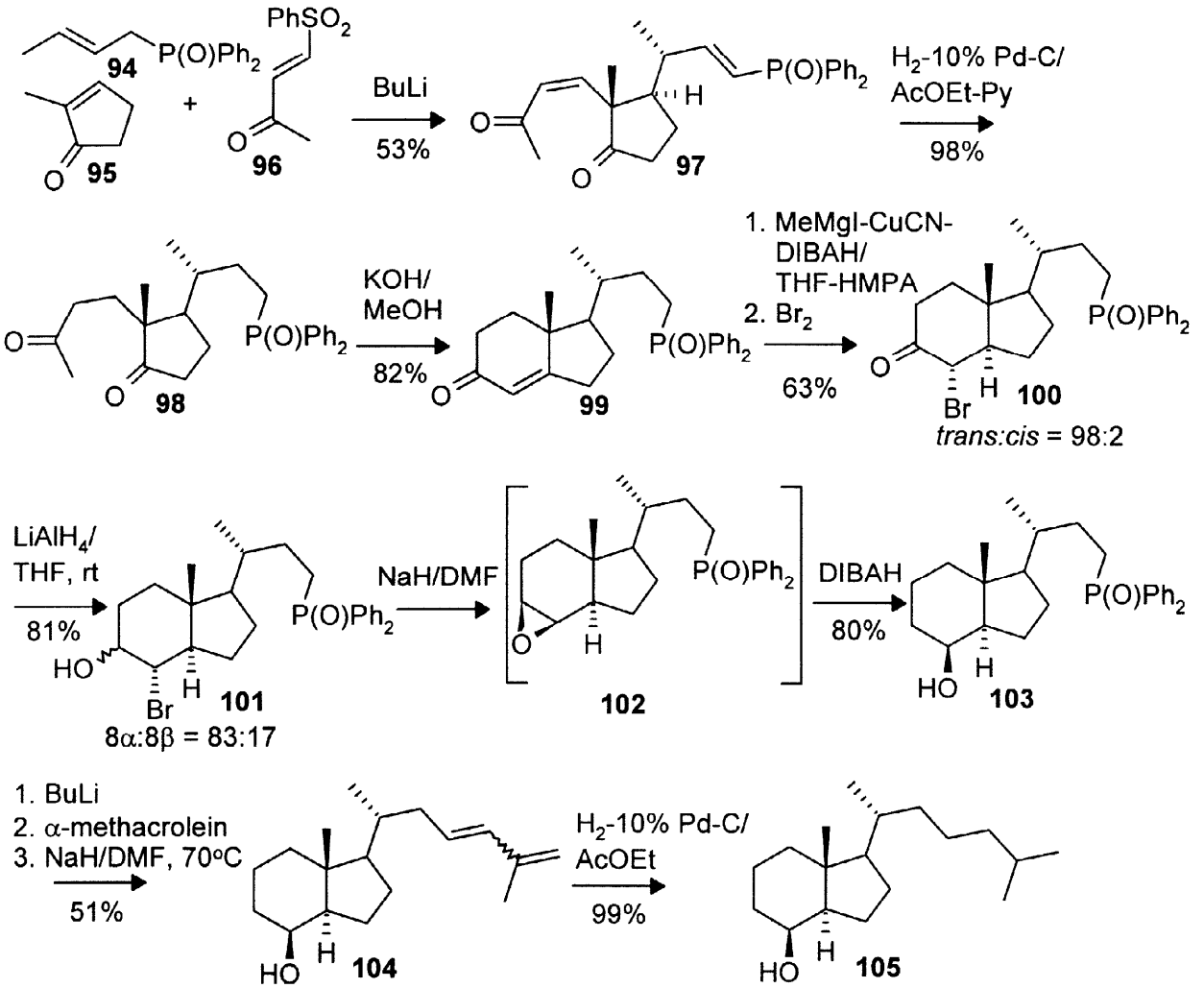
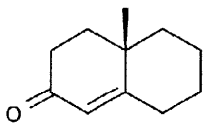
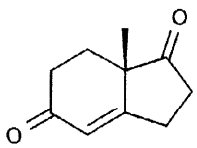
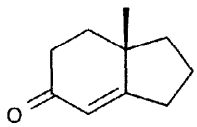
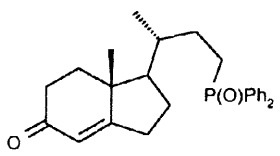


Table 5.

Reduction of unsaturated ketones with complex CuH reagents

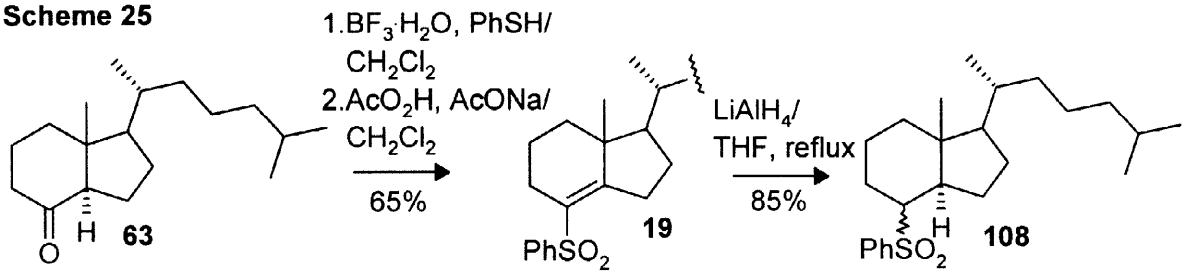
	Starting enone	Reagents and conditions	(yield), *cis*/ *trans* ratio	Ref.	Comments
1	 **106**	LiCuHpentyl THF-10%HMPA -20°C	(70%) **70:30**	90	1.reagent generated from CuI 2.H_2/Pd gave 4:1
2	 **26**	as above	(ca. 20%)	90	the isomer ratio was not determined
3	**106**	LiCuH(n-butyl) ether, -40°C	(80%) **70:30**	92	reagent from CuI
4	 **107**	MeCu-DIBAH THF-HMPA, 5:1 -50°C	(77%) **12:88**	93, 94	MeCu was generated from CuI and MeLi
5	**26**	^{t}BuLi(50mol%)-DIBAL, THF-HMPA, -50°C	(74%) **3:97**	96	similar results were obtained with ^{t}BuMgCl
6	 **99**	MeCu-DIBAH ether-THF-HMPA, -50°C	(70%) **2:98**	86	CuCN was used, the addition procedure was modified
7	**99**	BuCu-DIBAH ether-THF and then Br_2	(63%) **2:98**	86	HMPA was not required

3.4. Lithium aluminum hydride

Craig and coworkers[24] have found that vinyl sulfone **19** (Scheme 25, cf. Scheme 8) upon reduction with $LiAlH_4$ in THF at reflux temperature affords saturated sulfone **108** with a *trans*-ring junction.[100] The stereoselectivity and efficiency of this reduction has no precedent in the literature, although one or two examples of saturation of the double bond in vinyl sulfones with $LiAlH_4$ have been recorded.[101-103] The vinyl sulfone reduction

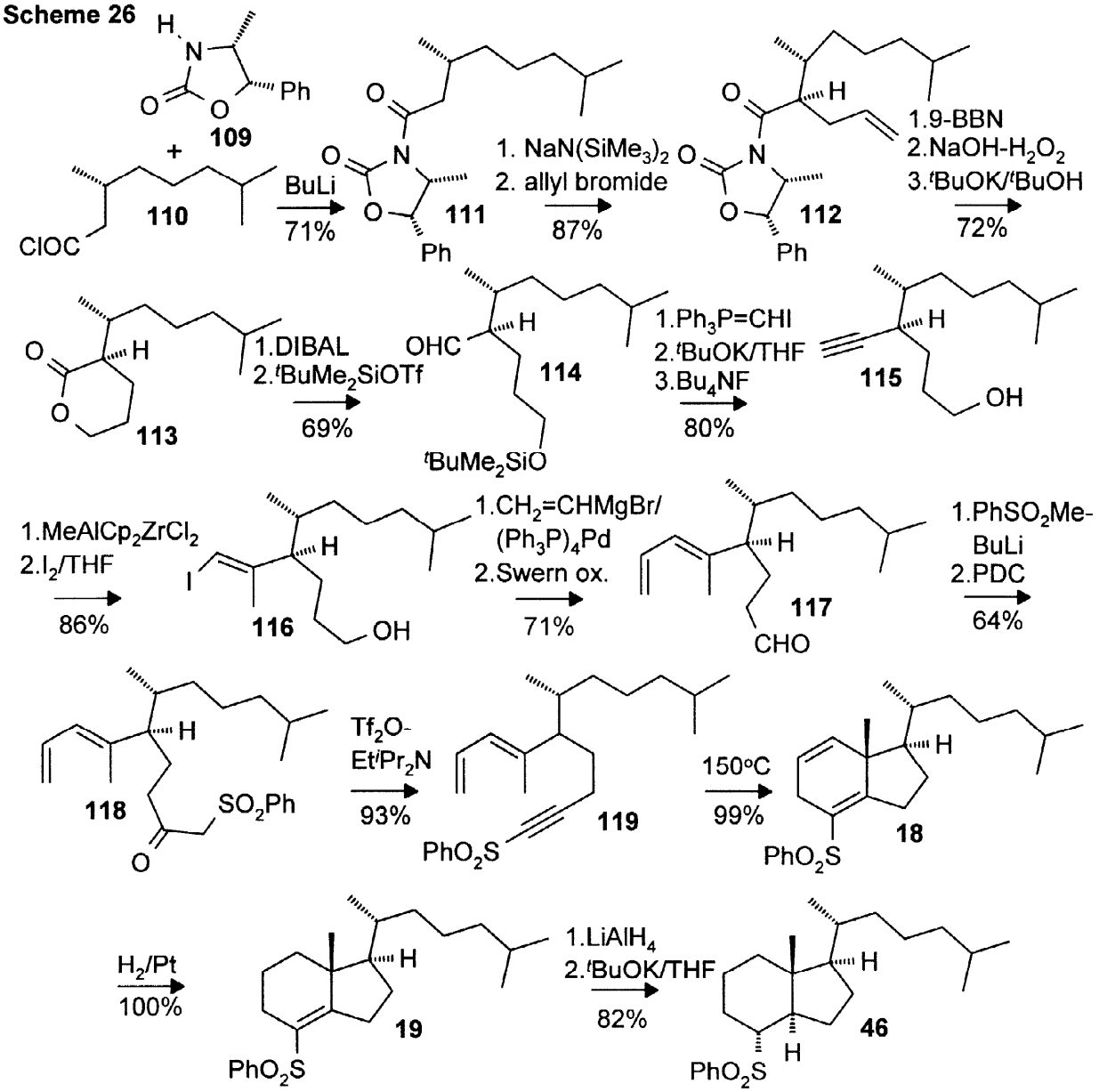
was then used[25] in an improved procedure for transforming ketone **63** into the corresponding 8-phenyl sulfonyl derivative **108** (Scheme 25).

Scheme 25



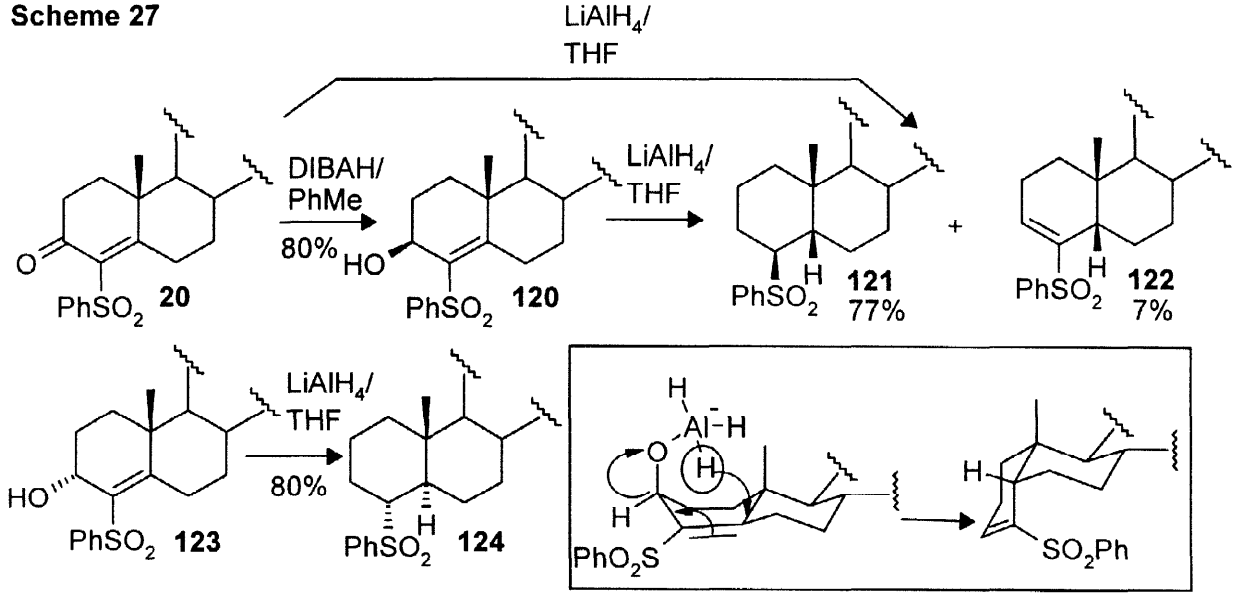
In a similar way, 25-hydroxy ketone (consisting mainly of the 14β-isomer) was transformed [104] into the 25-hydroxy 8-phenyl sulfonyl derivative using in the first step commercial (Aldrich) $BF_3 \cdot 2H_2O$.

Scheme 26



The stereoselective $LiAlH_4$ reduction of vinyl sulfone **19** was applied by Craig's and coworkers[24] to the synthesis of vitamin D hydrindane fragment **46** in which an intramolecular Diels–Alder reaction was used as the strategic step (Scheme 26). Optically active acid chloride **110** was obtained from (+)-pulegone *via* (+)-(*R*)-citronellic acid[105] in ca. 60% overall yield. Reaction of chloride **110** with the anion of oxazolidone **109** afforded the crystalline derivative **111** (Scheme 26). Allylation of **111** proceeded efficiently and diastereoselectively[106] to give alkene **112** (diastereomer ratio of >20:1). and thereby establish the C_{17} stereocentre. Hydroboration of **112** with oxidative work up gave the primary alcohol, which upon treatment with *t*-BuOK in *t*-butanol yielded lactone **113**. It is noteworthy that the efforts to remove the oxazoline chiral auxiliary by several intermolecular reactions failed. Reduction of the lactone **113** to the hydroxy aldehyde and protection of the hydroxy group gave the product **114**, which was subjected to *Z*-selective iodomethylenation[107] and the intermediate vinyl iodide was dehydroiodinated to give the acetylene derivative **115** (after deprotection of the hydroxy group). Negishi's[108] zirconocene dichloride mediated carboalanation of the acetylene **115** followed by trapping the intermediate alane with iodine afforded stereoselectively the vinyl iodide **116**. Palladium (0) mediated coupling of the vinyl iodide **116** with vinyl magnesium bromide followed by Swern oxidation of the hydroxy group afforded dienyl aldehyde **117**. Transformation of the aldehyde **117** into alkynyl sulfone **119** involved the addition of lithio(phenyl sulfonyl)methane and oxidation of the diastereomeric β-hydroxysulfones to give β-ketosulfone **118**, which was treated with triflic anhydride and Hünig's base.[109] Thermolysis of **119** yielded quantitatively a mixture of the bicyclic derivative **18** and its 13α-epimer (not shown in the scheme) of a 3:1 ratio (for further comments on intramolecular [4+2] cycloaddition of compound **119**, see Scheme 101 and the relevant text). After separation of the diastereomers by HPLC, the major isomer was subjected to catalytic hydrogenation. Only the disubstituted double bond was saturated. The *trans*-hydrindane system was generated selectively by reduction of **19** with $LiAlH_4$ to afford a mixture of saturated compounds with the equatorially (α-, 76%) and axially oriented (β-, 8%) benzenesulfonyl group. The β-sulfone was quantitatively epimerised upon treatment with *t*-BuOK in *tert*-butanol. The final optically active product was obtained in a ca. 3.4% yield from (+)-pulegone.

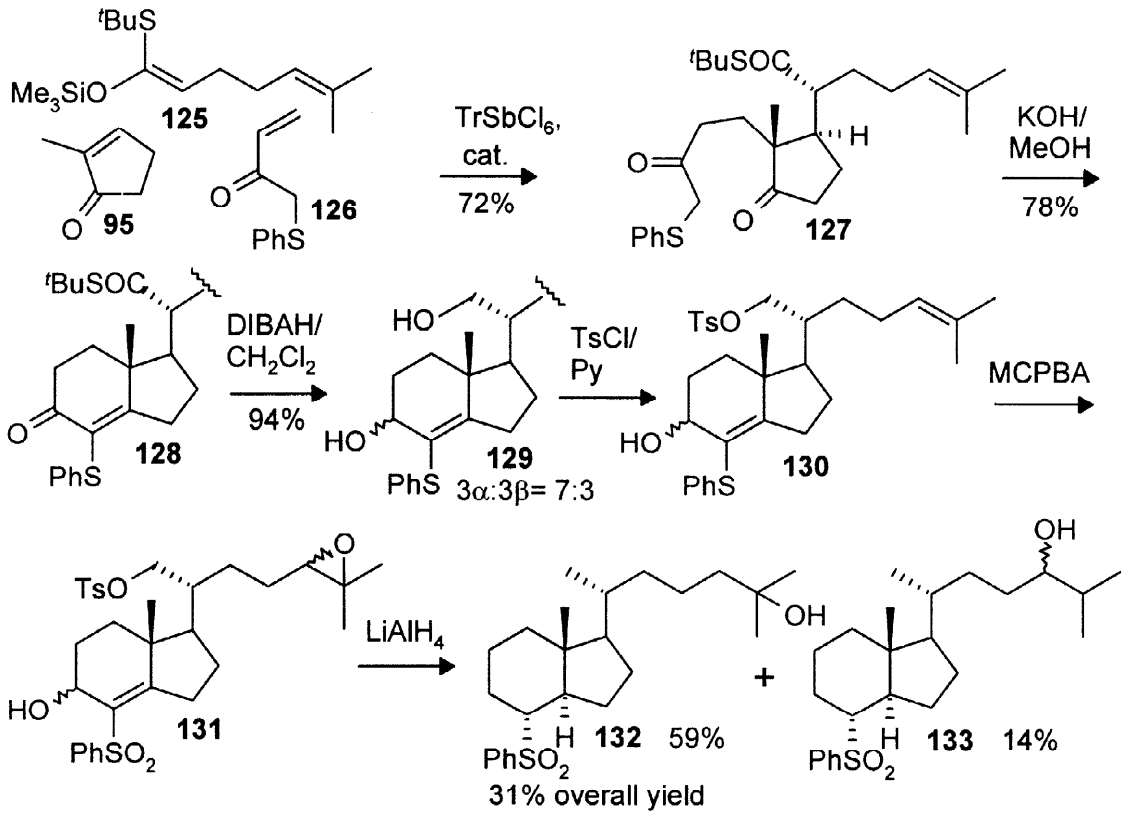
Scheme 27



Transformation of 4-phenylsulfonylcholest-4-en-3-one **20** (Scheme 27; for catalytic hydrogenation of **20**, see Scheme 8) into saturated and deoxygenated derivatives was examined in the present authors' laboratory [110] as a model for vitamin D total synthesis. Reduction of **20** with DIBAH smoothly yielded **120** (Scheme 27). Treatment

of **20** with $LiAlH_4$ in THF at reflux temperature afforded saturated sulfone **121** (77% yield) accompanied by some of vinyl sulfone **122**, which could be further reduced to **121**. A mixture of **121** and **122** of the same composition was obtained upon reduction of the 3β-ol **120** with $LiAlH_4$. However, reduction of the α-alcohol **123** with the same reagent afforded *trans*-decalin derivative **124**. These experiments indicated that the stereochemistry of reduction of the double bond in the allylic alcohols **120** and **123** was controlled by the hydroxy group orientation, most likely involving an intramolecular hydrogen delivery, as shown in Scheme 27.

Scheme 28



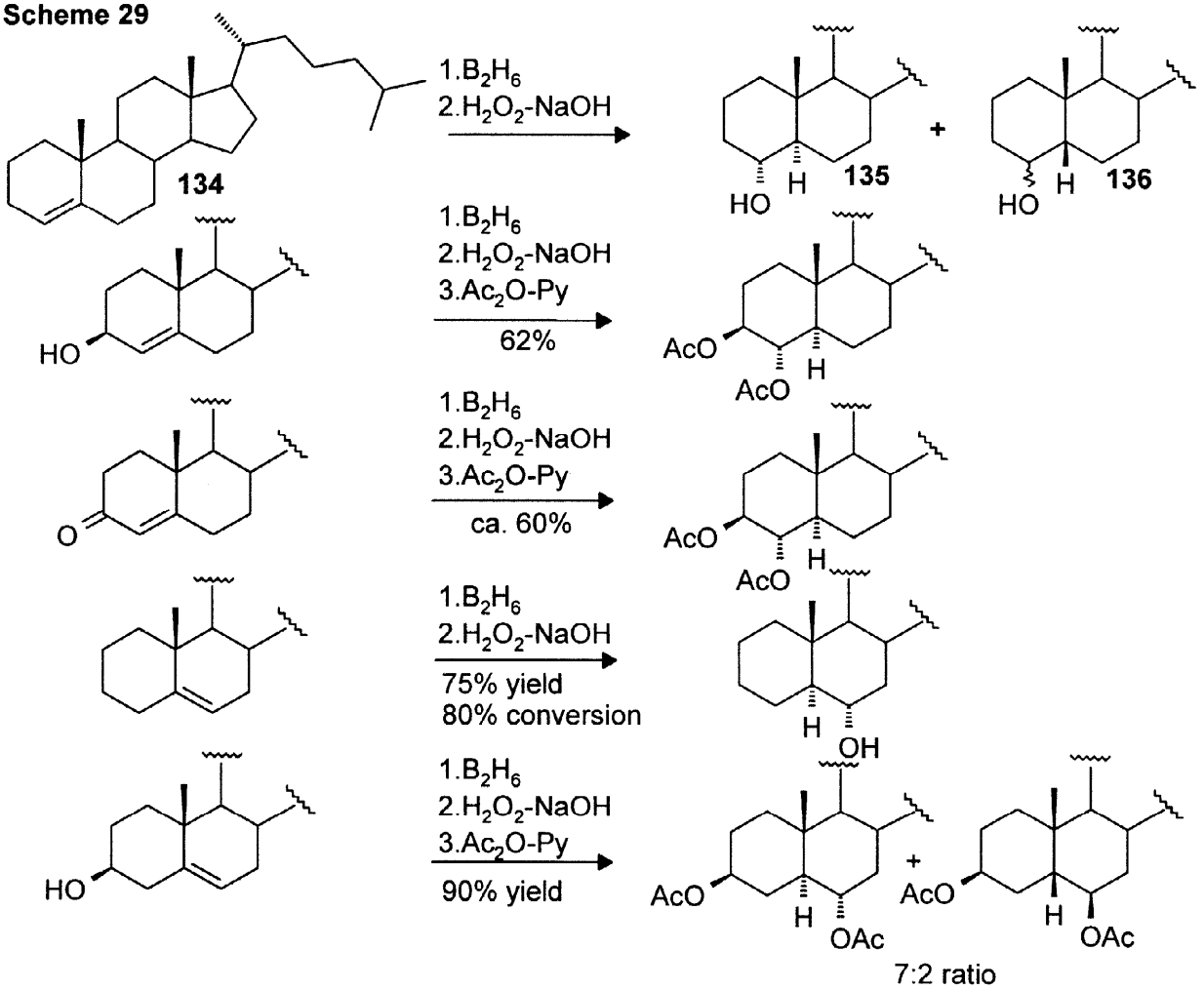
The synthesis of sulfone **132** [110] involving reduction of a vinyl sulfone moiety is presented in Scheme 28. Tandem Mukaiyama–Michael reactions of ketene acetal **125** first with 2-methylcyclopent-2-en-1-one **95** and then with 1-thiophenylbut-3-ene-3-one **126** afforded adduct **127** in 72% yield. Transformation of diketone **127** into **128** and then reduction of **128** with DIBAH gave diol **129** (a mixture of 8β- and 8α-epimers in a ratio of 7:3). The primary hydroxy function in diol **129** was selectively tosylated and the intermediate **130**, without isolation, was treated first with an excess of MCPBA and then with an excess of $LiAlH_4$ in THF. After chromatography, the hydroxy sulfone **132** was obtained in 59% yield along with a small amount of the 24-hydroxy derivative **133** (arising by the alternative opening of the C_{24}, C_{25}-epoxy function). It should be noted that contrary to the previously discussed model experiments with cholestane derivatives, reduction of the both 9α- and 9β hydroxy derivatives **131** gave the product **132** with a *trans*-ring junction. The synthesis of **132** involves 6 steps with three isolated intermediates and affords the final product in 31% overall yield from **125**.

3.5. Hydroboration

Hydroboration of cholest-4- and -5-ene derivatives was examined by Sondheimer and coworkers [111] (BH_3 was

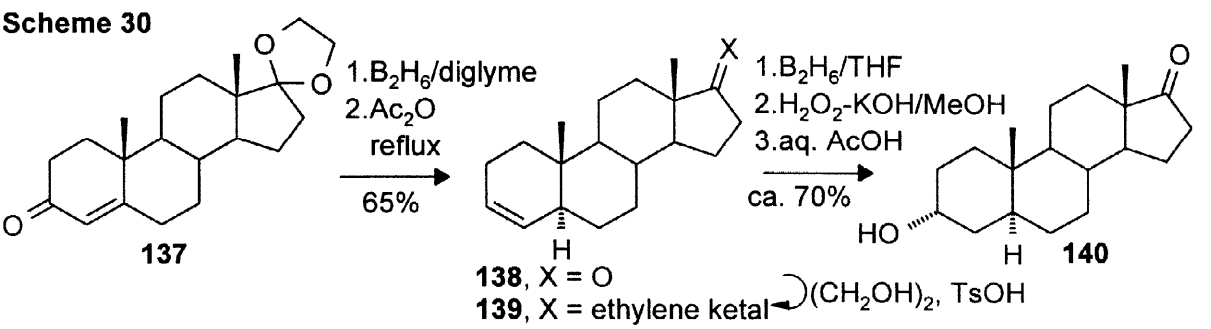
generated from $BF_3{\cdot}Et_2O$ and $LiAlH_4$; a mixture of THF and Et_2O was used as a solvent.). *syn*-Addition of diborane occurred in the *anti*-Markovnikov sense preferentially from the less hindered α-side of the molecule. Selected results are presented in Scheme 29. Hydroboration of cholesten-4-ene **134** was reported [111] to afford exclusively 5α-cholestan-4α-ol **135** (60% yield, 70% conversion). Similar results were recorded for androst-4-ene derivatives.[112] However, Bull *et al.*[113] found later that hydroboration of **134** leads to a mixture of **135** and **136** (most likely 4β) in almost the same amount (a ratio of 58:42).

Scheme 29



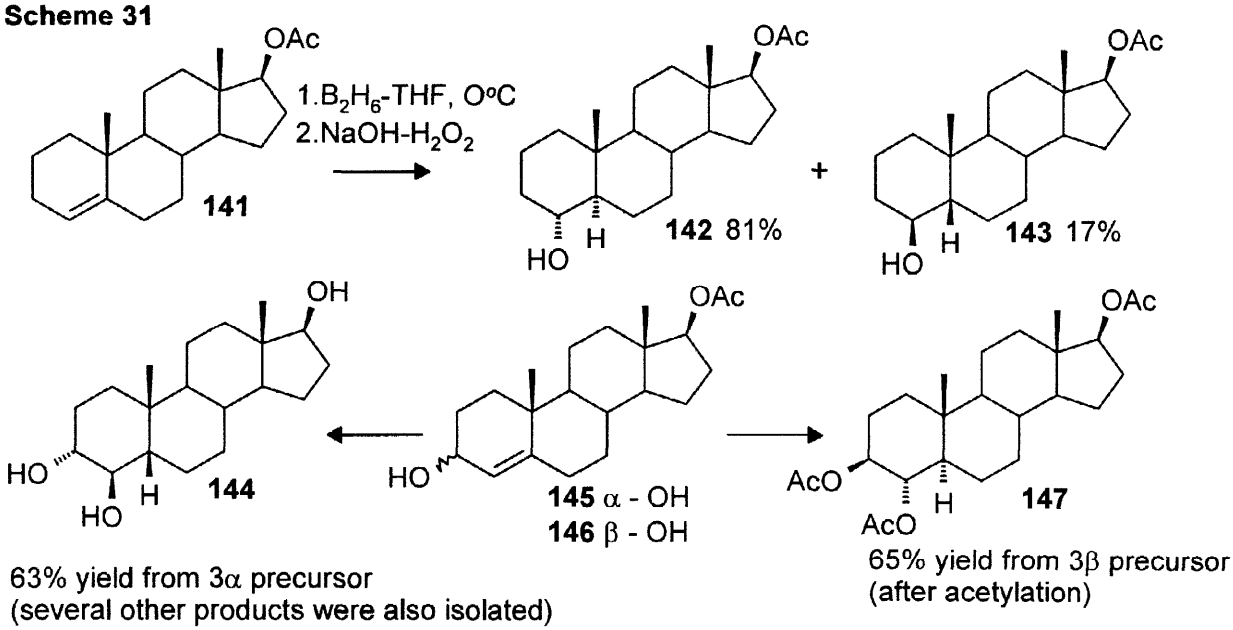
Caglioti *et al.*[114-116] have reported an efficient procedure for transforming steroidal 4-en-3-ones into the corresponding 5α-H-3-enes, involving hydroboration as the key step. Thus, hydroboration of **137** (Scheme 30), available from androst-4-en-3,17-dione, followed by treatment with Ac_2O, and reinstallation of the ketal moiety,

Scheme 30



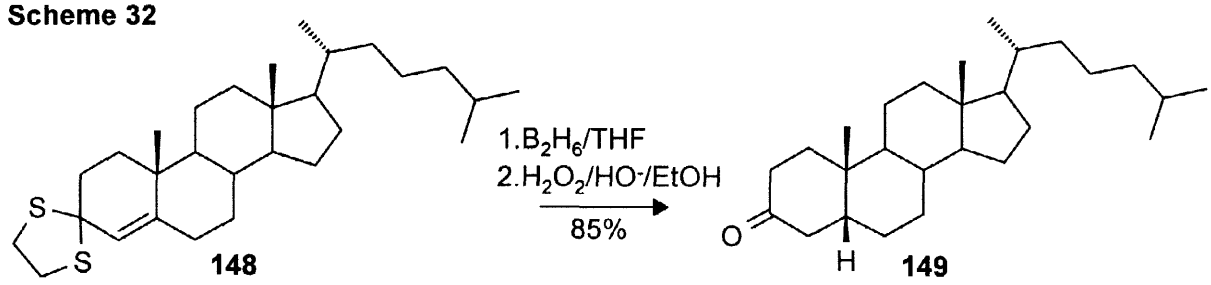
yielded **139** (65%, overall). The later was subjected to hydroboration and then oxidation to give **140** in 70% yield.[117]

Scheme 31



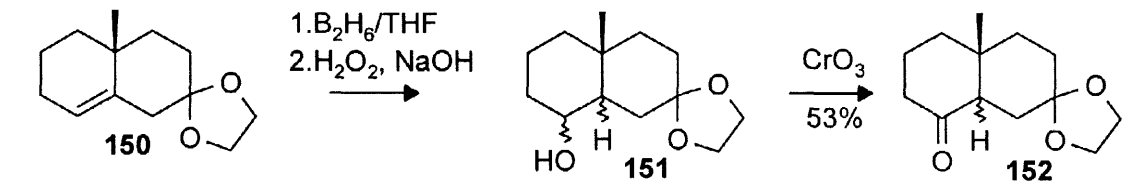
Hydroboration of some androst-4-ene derivatives has been recently investigated by Hanson *et al.*[118] using several compounds of the "normal", 19-nor and 9β-H,10α-H-series. Representative results are shown in Scheme 31. As can be seen, the 3α-hydroxy group directs the reagent towards the β-side of the molecule (**145** → **144**) while the 3β-hydroxy group has a relatively low effect on the reaction course (**146** → **147** as compared with **141** → **142**). On the basis of these results it was postulated that the 10-methyl group has a dominating role in controlling hydroboration of the 4,5-double bond. Hydroboration of 3α-hydroxy-5α-androst-14-ene has been briefly mentioned.[119] No stereochemical assignment was made.

Scheme 32



Reduction of cholestenone thioketal **148** with diborane afforded exclusively 5β-cholestan-3-one[120] **149** (Scheme 32).

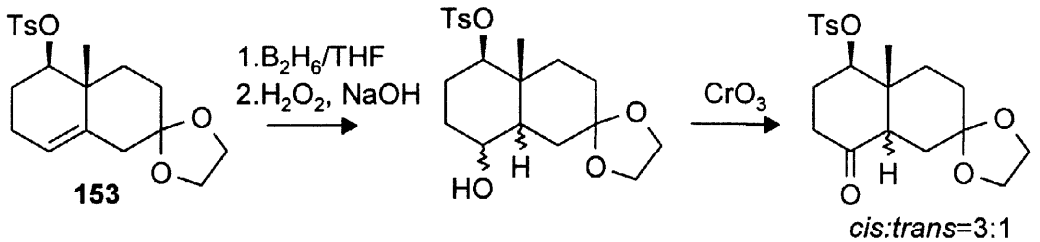
Scheme 33



epimerisation of **152**: TsOH/toluene, reflux, 65% yield, *cis:trans* =1:3
5% MeONa/ MeOH, 57% yield, *cis:trans* = 1:2

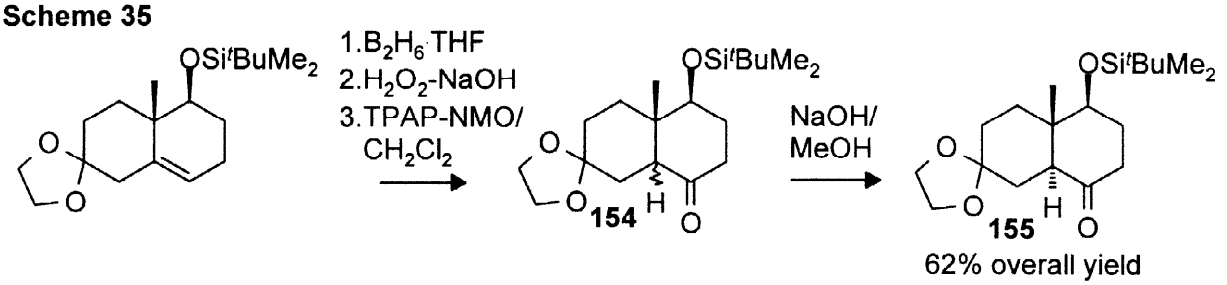
Ketal **150** upon hydroboration-oxidation gave [121] a mixture of isomeric alcohols **151** which, after oxidation and epimerisation of the respective ketones, afforded a mixture of *cis*-and *trans*-products **152**, as shown in Scheme 33.

Scheme 34



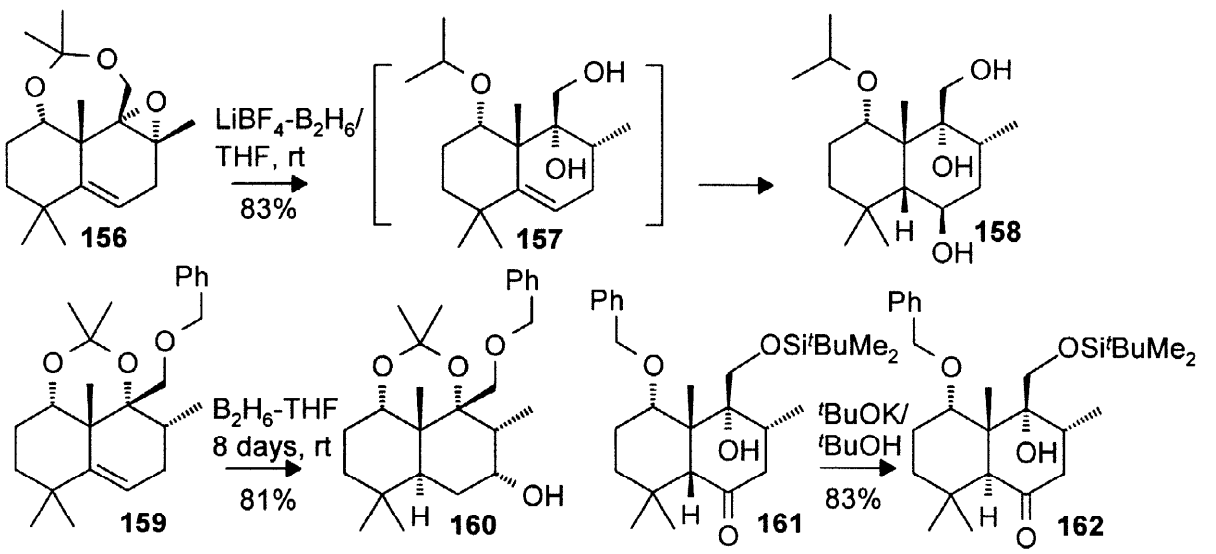
A mixture of epimers with the *cis* predominating was obtained on hydroboration of a similar compound[122] (**153**, Scheme 34). This mixture could not be equilibrated due to liability of the tosyloxy group.

Scheme 35



A more recent example of such a reaction[123] confirmed predominance of the *trans*-product **155** on equilibration of ketones **154**, Scheme 35. The ratio of hydroboration products was not determined.

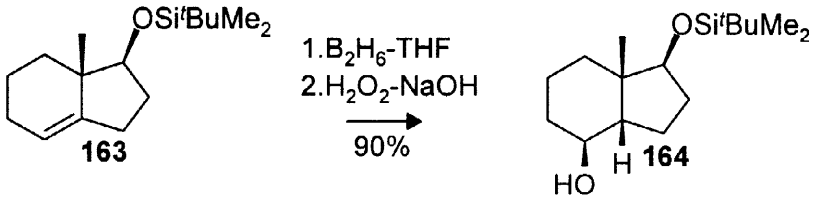
Scheme 36



Instructive examples of hydroboration of complex decaline derivatives have recently been reported in connection with forkolin synthesis.[124] Compound **156** (Scheme 36) resisted BH_3-THF but was efficiently hydroborated using $LiBF_4$-BH_3 in THF at room temperature to give **158**. It has been demonstrated that this reaction proceeds *via* the bicyclic intermediate **157** . Compound **157**, in contrast to **156**, reacted with BH_3-THF. The hydroboration occurred on the β-face of the molecule. The related ene **159** was hydroborated with BH_3 slowly to

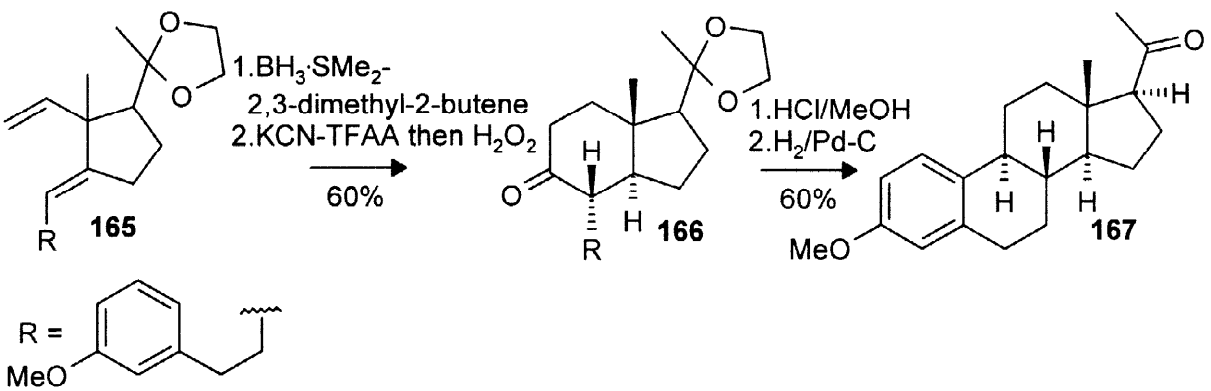
afford the *trans*-decalin derivative **160**. The authors assumed that migration of the double bond to the less hindered position occurred prior to hydroboration. Base-catalysed equilibration of *cis*-ketone **161** afforded the *trans*-product **162**.

Scheme 37



To the best of our knowledge, only one example of hydroboration of hydrindane derivatives with a double bond at the rings junction has been reported. Thus, hydroboration of 8,14-double bond in hydrindane **163** (Scheme 37) afforded the *cis*-fused derivative **164** as the exclusive product.[63]

Scheme 38

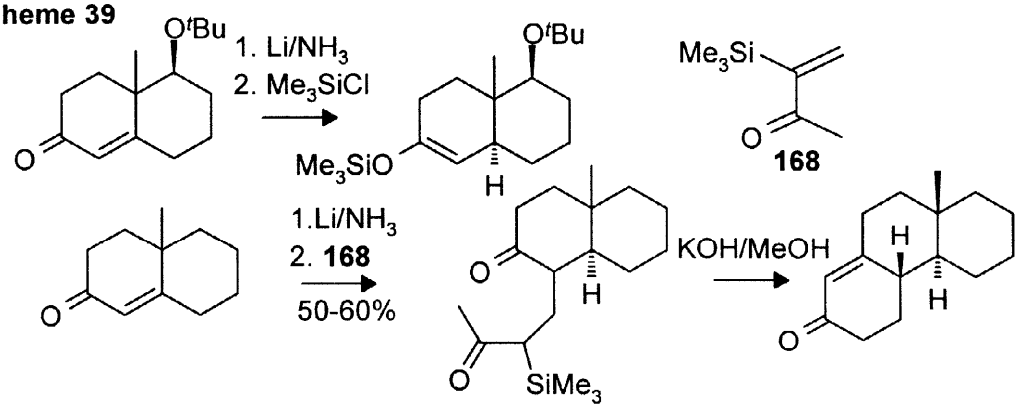


However, an ingenious application of hydroboration in estrone synthesis has been described.[125] Hydroboration of diene **165** (Scheme 38) with thexylborane generated in *situ*, followed by carbonylation and hydrolysis, gave *trans*-hydrindane **166**, which was transformed into estrone precursor **167** by the standard procedures.

3.6. Lithium in liquid ammonia reductions

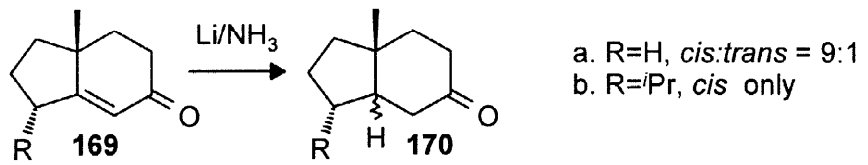
Lithium in liquid ammonia reduction[126] of steroidal 3-en-4-ones and decalin derivatives leads, as a rule,[127] to the *trans*-fused products. Application of this reduction to steroid total synthesis may be illustrated by the work of Boeckman [128] and Stork [129] (Scheme 39).

Scheme 39



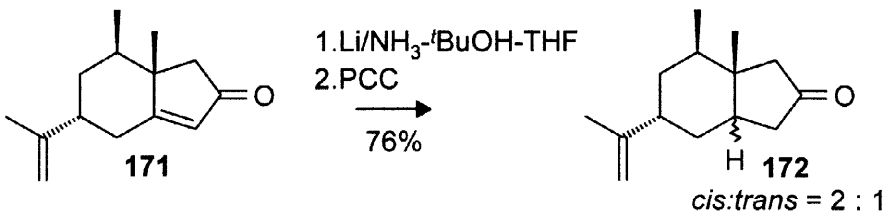
Lithium in liquid ammonia reduction of unsaturated ketone **169** R=H (Scheme 40) afforded a mixture of *cis/trans* products in a ratio of 9:1.[130] When the *iso*-propyl derivative was subjected to reduction only *cis*-**170** could be detected.[60]

Scheme 40



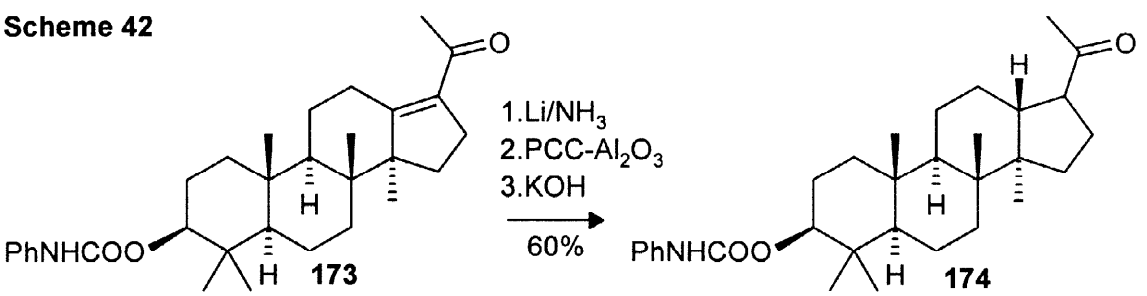
Reduction of **171** with Li in NH_3 has recently been reported.[131] It afforded a mixture of *cis*- and *trans*-isomers **172** in a ratio of 2:1 (Scheme 41, cf. Scheme 17).

Scheme 41



Lithium/liquid ammonia reduction[132] of enone **173** with methyl groups at C_8-β and C_{14}-α occurred with hydrogen addition on the β-face of the molecule to give the *trans*-hydrindane derivative **174** (Scheme 42).

Scheme 42



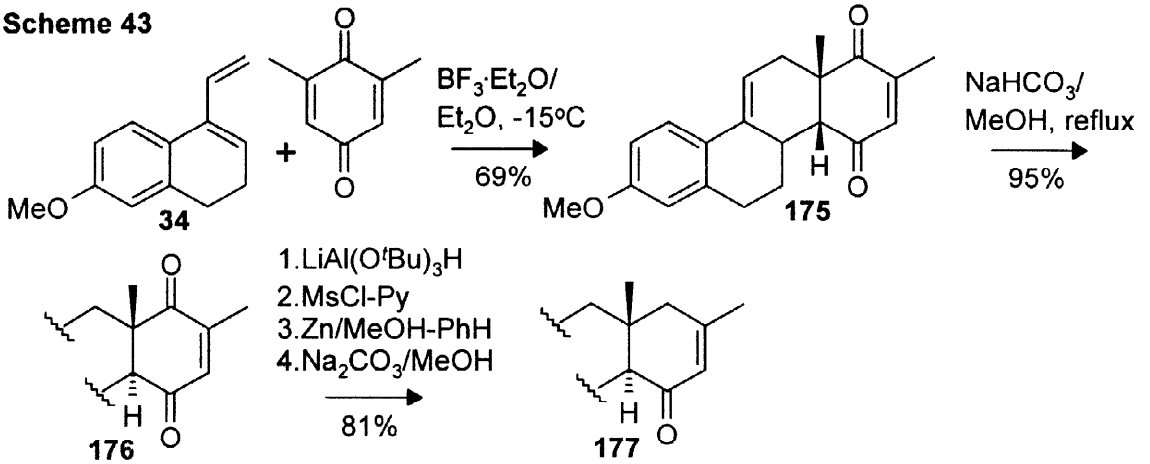
3.7. Comments on the equilibration of bicyclic systems with an oxo group at the α-position to the ring junction

Cholestan-4-one and cholestan-6-one on equilibration with methanolic KOH afforded mixtures containing 99.1±2% and 88.4±2 of the respective *trans*-isomer.[133,113] Thermodynamic preference of the *trans*-A/B ring junction in cholestane derivatives is well known. However, the equilibrium position may be dramatically affected by the presence of some substituents; for example, on treatment of 5α-androstan-1,4,17-trione with methanolic KOH, the corresponding 5β-triketone was obtained in 82% yield.[134]

Equilibration of decalin derivatives with the carbonyl group in α-position to the ring junction followed by a ring contraction was used to establish a *trans*-hydrindane system in the Woodward steroid synthesis.[135-137] Several applications of the ring contraction technique to steroid synthesis have been developed. The approach of Valenta and coauthors[138] to estrone derivatives, presented in Scheme 43, illustrates this method. *cis*-Dione **175**, obtained from the acid-catalysed Diels–Alder reaction of diene **34** and 2,6-dimethylbenzoquinone, was isomerized with $NaHCO_3$ in refluxing methanol to give in high yield the *trans*-product **176**. Further transformations involved

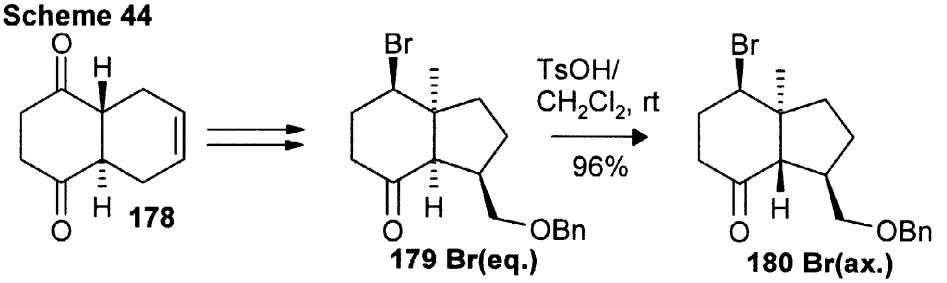
removal of the 17a oxo-group to give the intermediate **177**.

Scheme 43



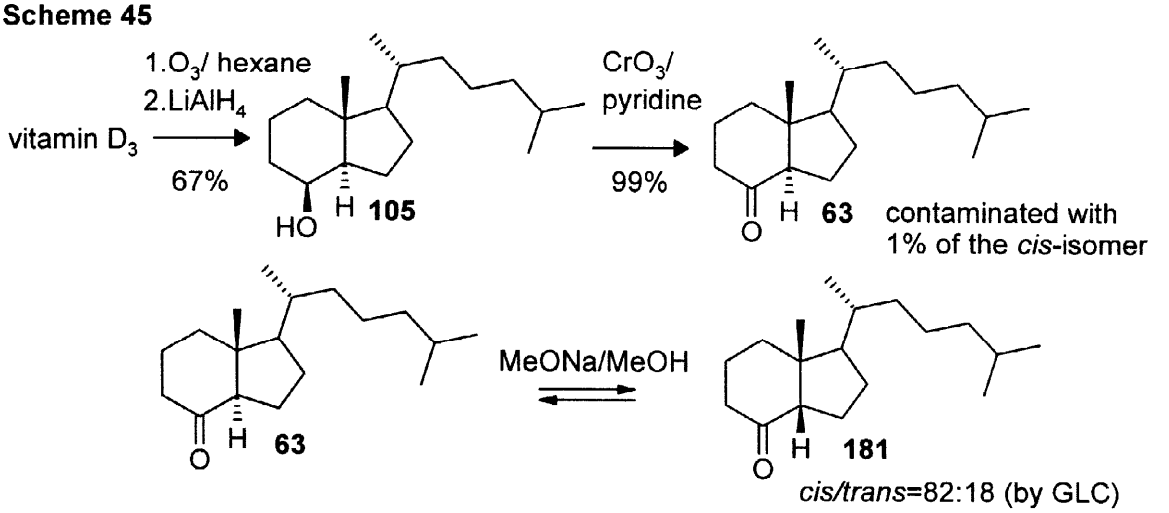
An interesting *trans*-decalin to *trans*-hydrindane transformation was devised by Masamune and co-workers for the synthesis of *rac*-prepinnaterpene, a brominated diterpene of marine origin.[139] Bromo ketone **179** (Scheme 44) with *cis*-fused rings, obtained from easily available[140,141] *trans*-octalin-1,4-dione **178**, upon treatment with TsOH (but not with PPTS) underwent isomerization to the *trans*-analogue **180** (*cis:trans* = 1:18). The bromine atom is equatorial in **179** but axial in **180**.

Scheme 44



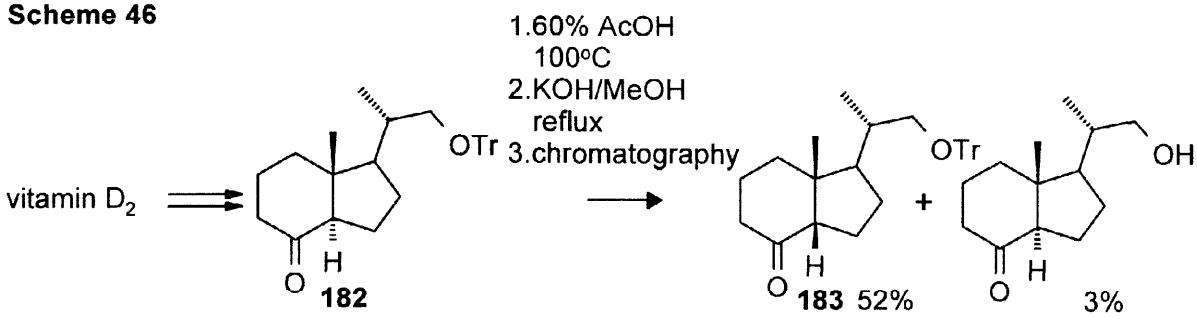
In the absence of non-binding interactions (such as the bromine in the previous example) equilibration of hydrindane derivatives usually affords mixtures of *cis*-and *trans*-isomers, with the former predominating. Treatment of 5α-androstan-15-one with methanolic NaOH followed by chromatography yielded the pure 14β-H derivative.[142] The equilibrium position under these conditions was estimated as 14α-H:14β-H=13-15:87-85.

Scheme 45



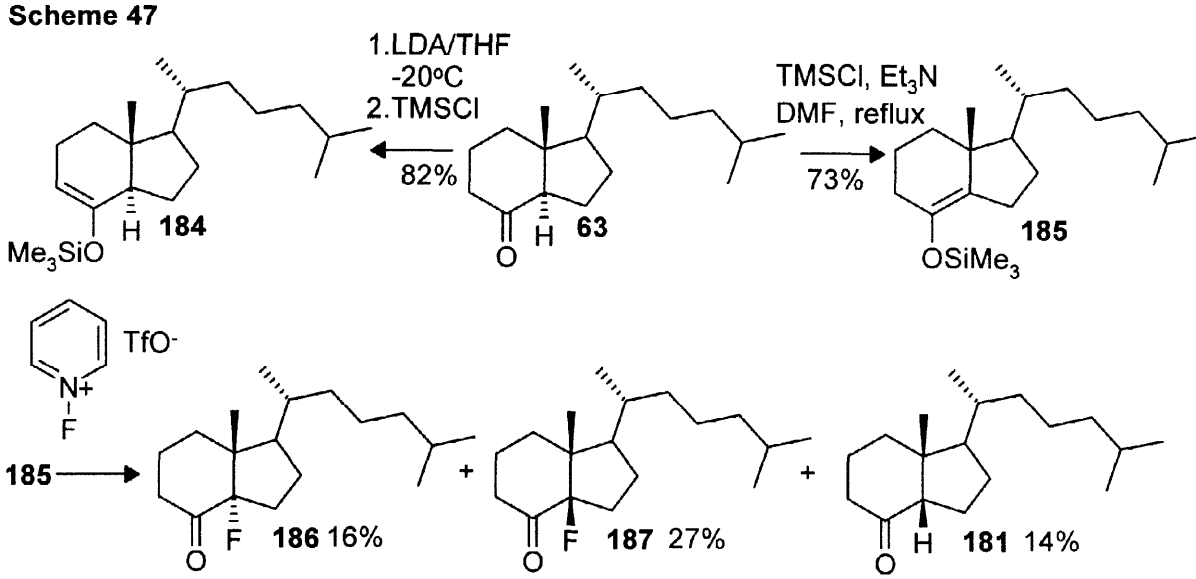
Peterson and coworkers investigated[143] the preparation of *trans*-ketone **63** from vitamin D_3, and its epimerisation at C_{14}. The best results were obtained when hexane was used as a solvent for ozonolysis, the crude ozonide was reduced with $LiAlH_4$, and then alcohol **105** (Scheme 45) was oxidized with CrO_3 in pyridine.[144-146] Under these conditions the product **63** was obtained in 66% yield, contaminated with only 1% of the *cis*-isomer. It was found that epimerisation of ketone **63** with MeONa in MeOH leads to a mixture of *cis*-and *trans*-products (**181**) in a ratio of 82:18. These authors have performed MM2 calculations to determine the *cis/trans* equilibrium position for model hydrindan-8-one derivatives, among others for that with the isopropyl group at C_{17}.[147,148] It has been concluded that the calculations underestimate the contribution of *cis*-isomers in most cases.

Scheme 46



Epimerisation of **63** with CF_3CO_2H in benzene affords a mixture of *cis*-and *trans*-isomers in a ratio of 81:19, of which pure components were isolated by chromatography in 58 and 10% yields, respectively.[146] Base-catalysed epimerisation of 14-oxo-derivative **182** afforded[149] *cis*-product **183** (52% yield) and a small amount of starting ketone (Scheme 46).

Scheme 47



Dauben and Greenfield[150] have described the fluorination of ketone **63** *via* either the kinetic or thermodynamic trimethylsilyl ethers, **184** and **185** respectively (Scheme 47). Enol ether **185** on treatment with N-fluoropyridinium triflate[151,152] in CH_2Cl_2 at room temperature yielded 14α- and 14β-flouro derivatives, **186** and **187**, in a ratio of 1:1.7, along with non-fluorinated 14β-H ketone **181** and some 8-oxo-14-ene (not shown in the scheme). A somewhat higher proportion of the respective *cis* product was obtained on reaction of an enol ether similar to **185** with phenylselenyl chloride (2.5:1 *cis/trans* ratio).[63]

Transformation of 8-oxo-14β-H vitamin D hydrindane derivatives into useful 14α-H precursors of vitamin

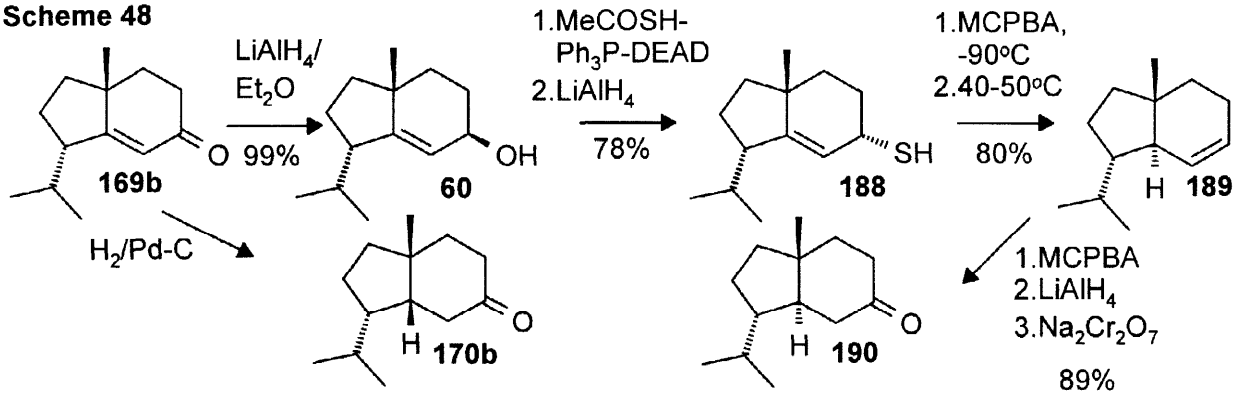
D has been described (cf. Schemes 18 and 25 and the relevant text).

4. Reductions with intramolecular hydrogen delivery

4.1. Sulphinic acid fragmentation

Corey and Engler[60] reported the synthesis of *trans*-hydrindanone **190** from α,β-unsaturated ketone **169b**, involving intramolecular hydrogen delivery. Thus, reduction of the carbonyl group in **169b** (Scheme 48) occurred stereoselectively to afford the derivative with the β-hydroxy group **60**. The Mitsunobu reaction[153] of **60** with thiolactic acid followed by $LiAlH_4$ reduction yielded thiol **188**, with inversion of the configuration. Oxidation of thiol **188** with MCPBA at -90 °C gave the sulphinic acid derivative which upon heating to 40 - 50 °C underwent thermal decomposition[154,155] to form olefin **189**. Further transformation of **189** into **190** involves: epoxidation with MCPBA; epoxide opening with $LiAlH_4$ to form a mixture of alcohols in a ratio of 3:1; and oxidation of the alcohol mixture. *trans*-Hydrinadnone **190** was obtained in 55% overall yield in a six step synthesis (cf. Schemes 17 and 40).

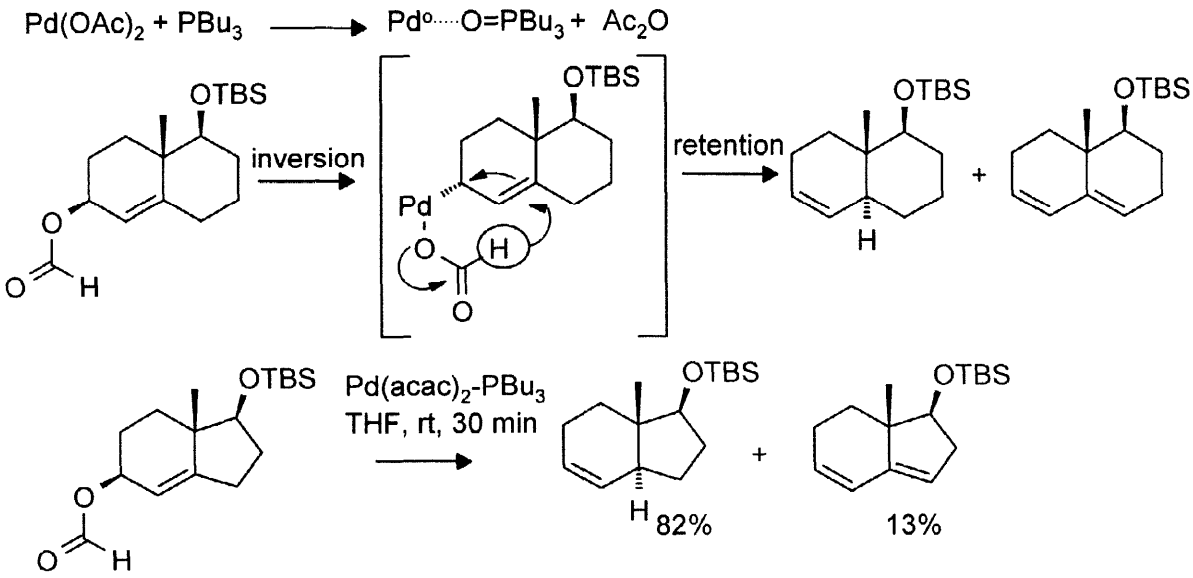
Scheme 48



4.2. Palladium-catalysed hydrogenolysis of allylic formates

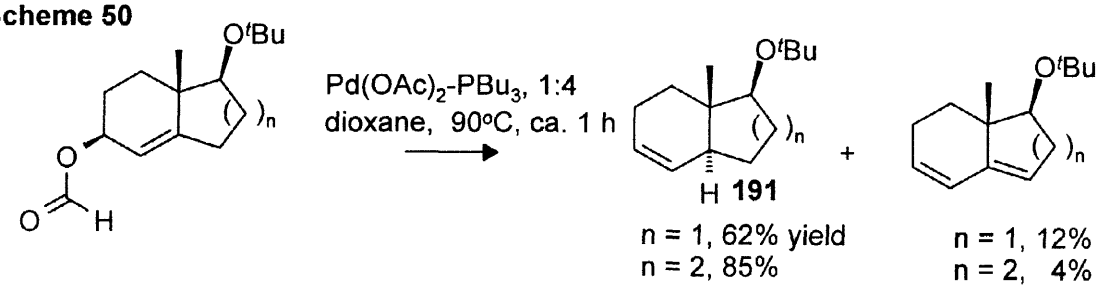
A general synthetic approach to *trans*-fused decalin and hydrindane systems consists of palladium-catalysed hydrogenolysis of formates[156] of the relevant allylic alcohols, developed by Mandai, Tsuji and their coworkers.[157] The catalyst was prepared from equimolar amounts of $Pd(OAc)_2$ or $Pd(acac)_2$ and PBu_3 in THF. Some of the results

Scheme 49



reported by those authors together with the stereochemical explanation are presented in Scheme 49. The active catalyst is formed by reduction of Pd^{II} with PBu_3. Allyl formates in decalin or hydrindane systems underwent fragmentation with stereoselective hydrogen atom transfer and translocation of the double bond.

Scheme 50



Tietze and Subba Rao[158] failed to reproduce the formate hydrogenolysis under the conditions discussed above. However, when the proportion of $Pd(OAc)_2$ and PBu_3 was changed and the reaction was carried out in dioxane at 90 °C the fragmentation products were obtained in good yield (Scheme 50). *trans*-Hydrindene **191** was further used for steroid synthesis by routes involving the Heck olefination or conjugate addition and then ene reaction.[159]

The palladium-catalysed fragmentation of allylic formates has been used extensively in the present authors' laboratory. Tributylphosphine, 99%, purchased from Strem Chemicals, was used. Under the conditions recommended by the German authors, the hydrindane derivatives afforded the 8,9-enes along with the corresponding dienes, in a ratio of ca. 2:1. The representative results[160,161] are shown in Scheme 51 and Table 6.

Scheme 51

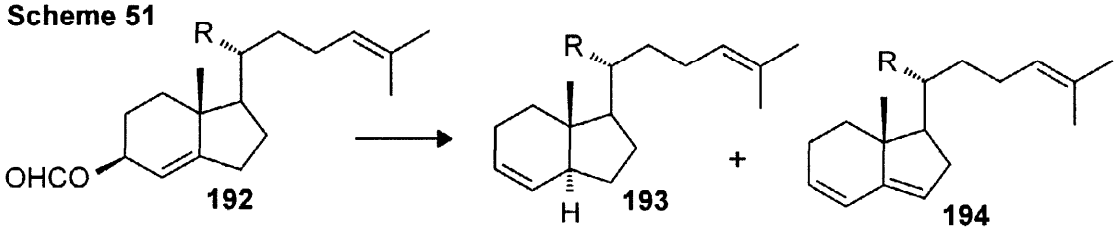


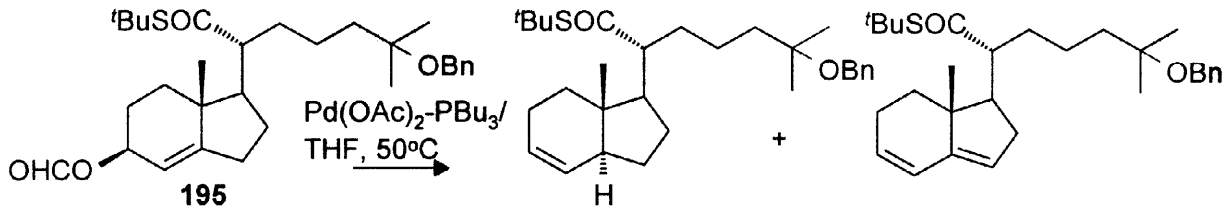
Table 6.

Palladium-catalysed hydrogenolysis of allylic formates **192**

R	**193**, yield(%)	**194**, yield(%)
CH_2OCHO	54	29
CH_3	63	29
CH_2OTBS	57	32
COS^{t}Bu	62	31

It was found that the reaction is sensitive to trace contaminants in the tributylphosphine such that different batches showed different activity. With the best samples of phosphine the results reported by the Tsuji group were reproducible. With this tributylphosphine, hydrindane derivative **195** (Scheme 52) was smoothly transformed into the decarboxylate product (93% yield, ene:diene in a ratio of 3.7:1).[26]

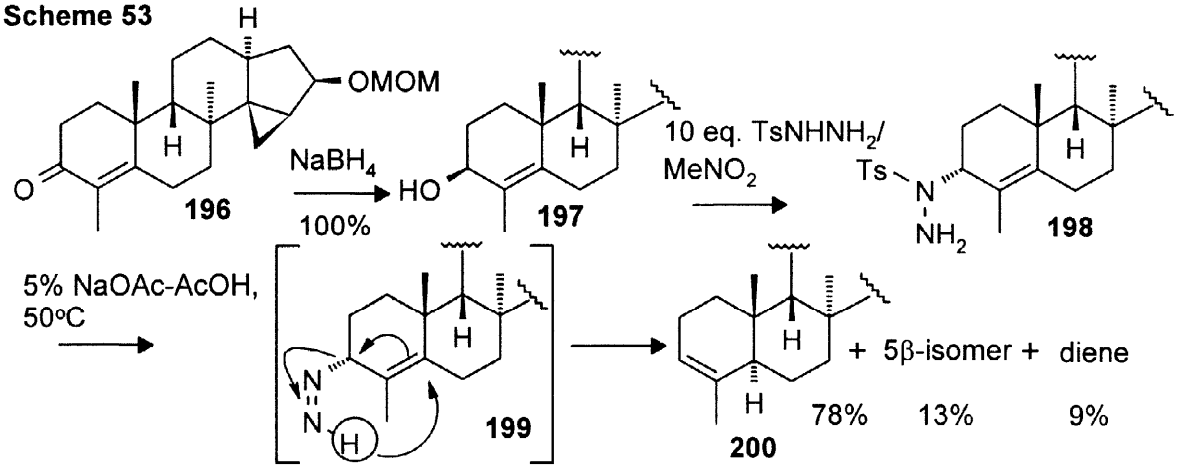
Scheme 52



4.3. Reductions involving diazene (diimine) derivatives

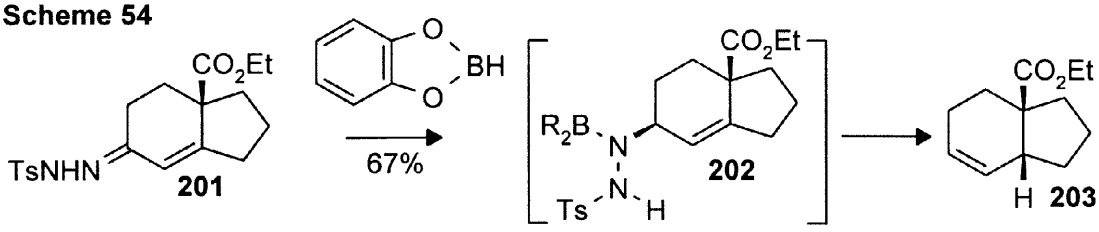
A method for stereocontrolled reduction by hydride transfer from a diazene moiety[162] was devised by Corey and Virgil[163] in the course of protosterol synthesis. The intermediate 4-methyl-4-en-3-one **196** (Scheme 53, please note the 8α,9β configuration) was reduced to the 3β-hydroxy derivative **197**, which was reacted with an excess of *p*-toluenesulfonylhydrazide in nitromethane to afford the 3α-hydrazine derivative **198** which in turn was briefly warmed in AcOH containing 5% AcONa to generate *in situ* diazene **199**. The release of nitrogen gave the product, which consisted of the required 3-ene **200** (78%), small amounts of the corresponding 5β-isomer and the diene.

Scheme 53



A related method for reduction of an allylic alcohol *via* allylic hydrazine derivative and its oxidation to the respective diazene was reported earlier by Corey and coworkers.[164]

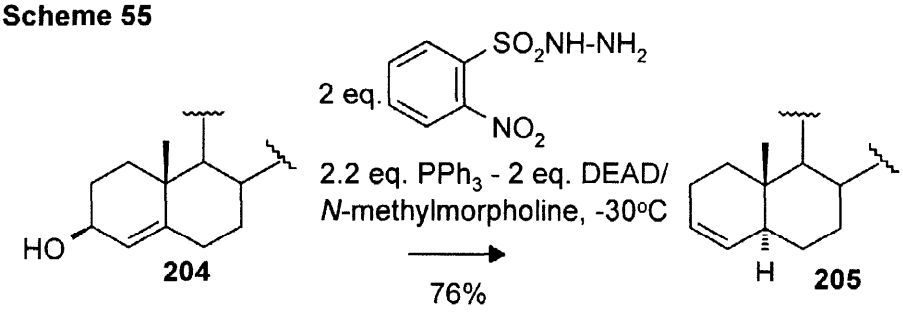
Scheme 54



Reduction of α,β-unsaturated ketones (Scheme 54) via their tosylhydrazones was reported by Greco and Maryanoff.[165] Thus, treatment of **201** with catecholborane proceeds presumably with addition of the hydride anion from the α-face of the molecule to generate **202**. Elimination of the tosyl group and the borane residue affords the β-oriented diazene group, which undergoes fragmentation with intramolecular hydrogen delivery to give **203**.

Reduction of cholest-4-en-3-one tosylhydrazone with $NaBH_3(CN)$ afforded a mixture of 5α- and 5β-3-enes in a ratio of 1:5 with 39% yield, and a mixture of cholestanes (61%).[166]

Scheme 55



Recently, an improved method for the reductive transposition of ethylenic bonds in allylic alcohols with *in situ* generated diazene was reported.[167] The authors recommend the use of *o*-nitrobenzenesulfonylhydrazine for the Mitsunobu-type substitution of the hydroxy group and the use of *N*-methylmorpholine as the solvent. Transformation of cholest-4-en-3β-ol **204** into 5α-cholestane **205** (Scheme 55) is one of the examples of efficient transformations under such conditions.

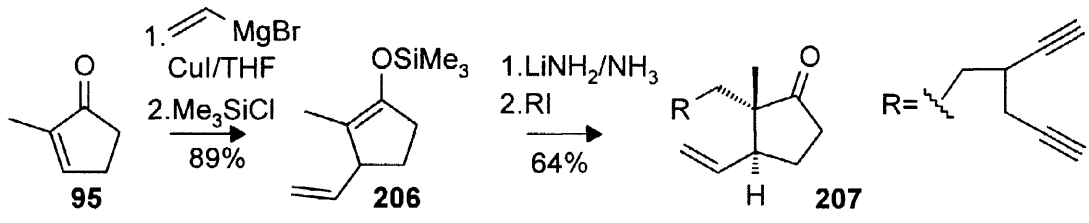
Other useful synthetic applications of intramolecular reactions with diazenes were also reported recently.[168,169]

5. Conjugate additions, alkylations and related reactions

5.1. Intermolecular conjugate addition

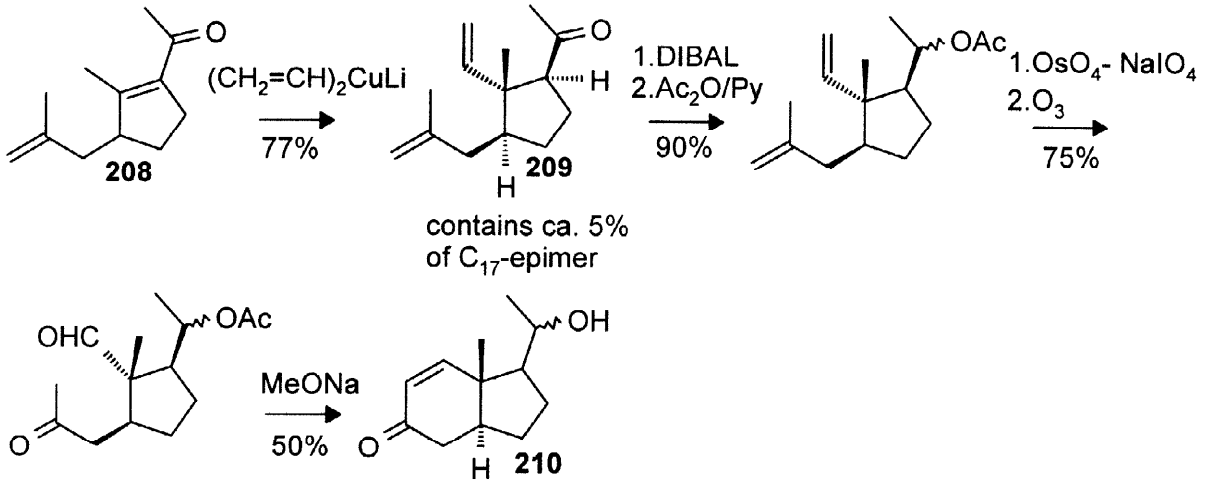
Pioneering work on two consecutive carbon-carbon bond forming reactions involving conjugate addition and enolate trapping has been carried out by Stork[170,171] Boeckman Jr.[172] and other authors.[173] To the best of our knowledge this method was first applied to *trans*-hydrindane construction by Funk and Vollhardt.[174] Copper(I)-promoted conjugate addition of vinyl magnesium bromide to 2-methylcyclopent-2-ene-1-one **95** and conversion of the enolate to its trimethylsilyl derivative gave **206** (Scheme 56). Lithium amide in liquid ammonia[175] promoted alkylation of **206** with acetylenic iodide and afforded the product **207** in 64% yield as a mixture of *cis*- and *trans*-isomers in a ratio of 1:2. When ethyl bromoacetate was used[176] as the trapping agent the adduct (**207**, R=CO_2Et) was obtained in 81% yield with slightly better diastereoselection, ca. 1:3. The acetylenic intermediate **207** was further used for remarkable cobalt catalysed cyclotrimerization to afford ultimately estrone. Since then the conjugate addition-enolate trapping technique has been frequently used for *trans*-hydrindane construction, providing in several cases appreciably higher diastereoselectivity.

Scheme 56



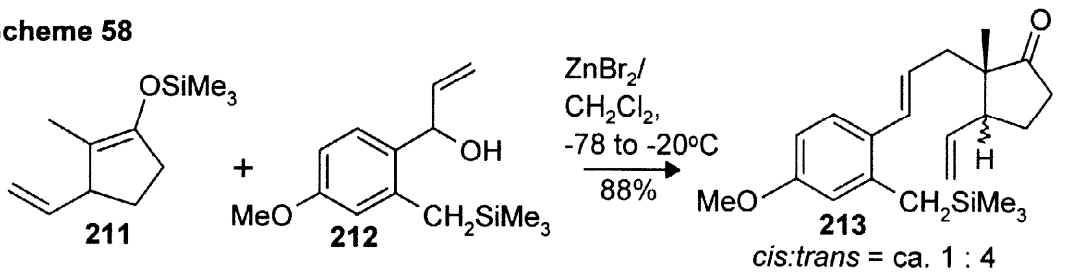
Conjugate addition of vinyllithiumcuprate[177] to α,β-unsaturated ketone **208** yielded compound **209** with high diastereoselectivity [178] (Scheme 57). The product **209** was easily transformed into *trans*-hydrindane derivative **210**, which was further used in cortisone synthesis.

Scheme 57



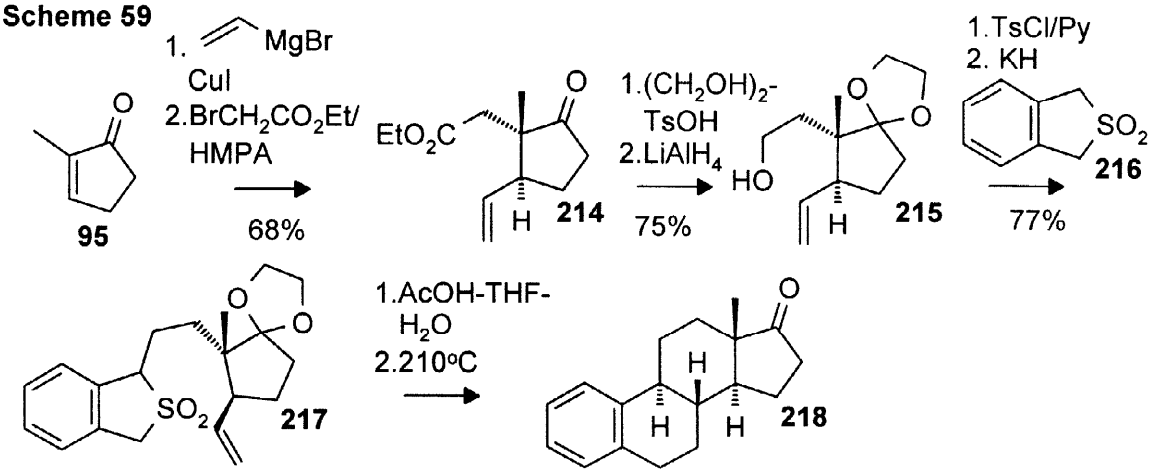
Enolate **211** (Scheme 58) was reacted with allylic alcohol **212** in the presence of a catalytic amount of $ZnBr_2$[174c] to give mostly the *trans*-product **213** (Scheme 58). The *trans*-derivative **213** was transformed into estrone.

Scheme 58

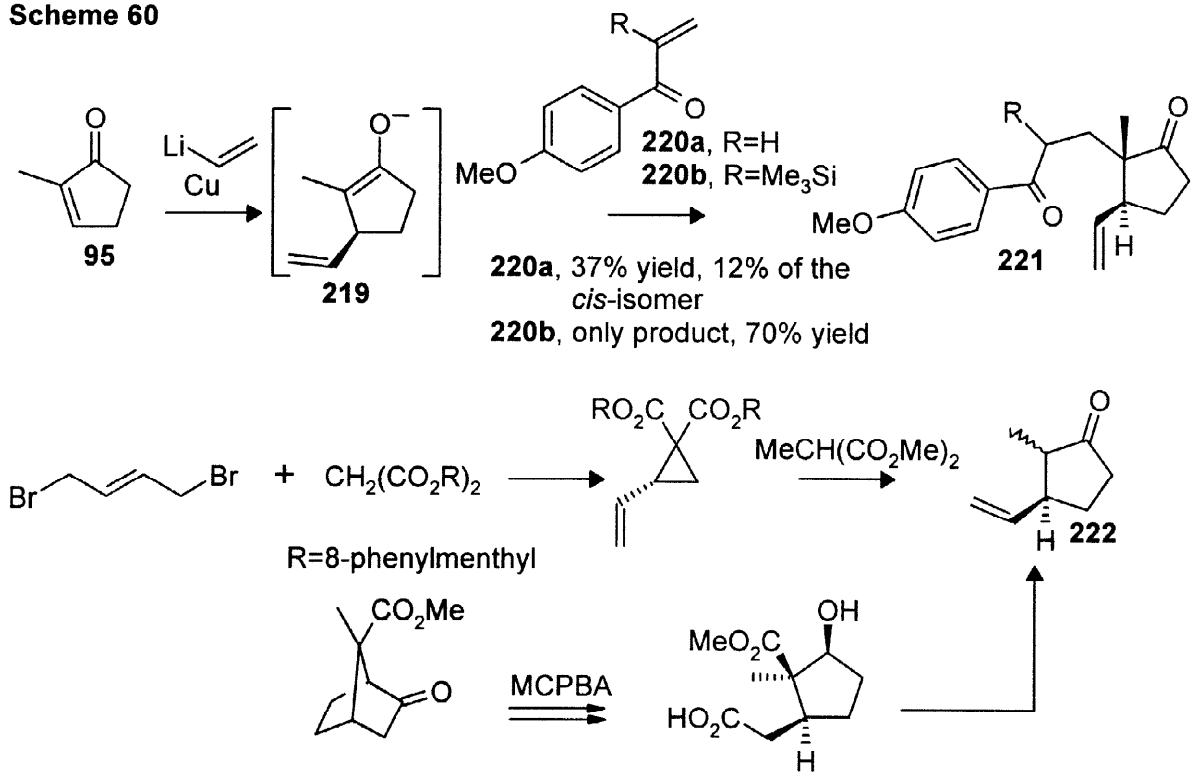


In a similarly short approach to estrone, the CD fragment was prepared by conjugate addition of vinylmagnesium bromide to methylcyclopentenone followed directly by alkylation of the intermediate (magnesium) enolate with ethyl bromoacetate.[179] (cf. Scheme 56). Product **214** (Scheme 59) was obtained as a mixture of *cis*- and *trans*-isomers (ca. 1:3.5). The coupling of the tosylate derived from alcohol **215** with the rings A/B precursor **216** and thermal fragmentation of the intermediate **217** afforded product **218** contaminated with 5-7% of the C/D *cis*-isomer. It should be noted that the use of *t*-butyl bromoacetate with HMPA under otherwise similar conditions was reported[180] to provide the adduct with an excellent diastereoselectivity (96% of the *trans*-isomer), but the yield was lower (47%).

Scheme 59

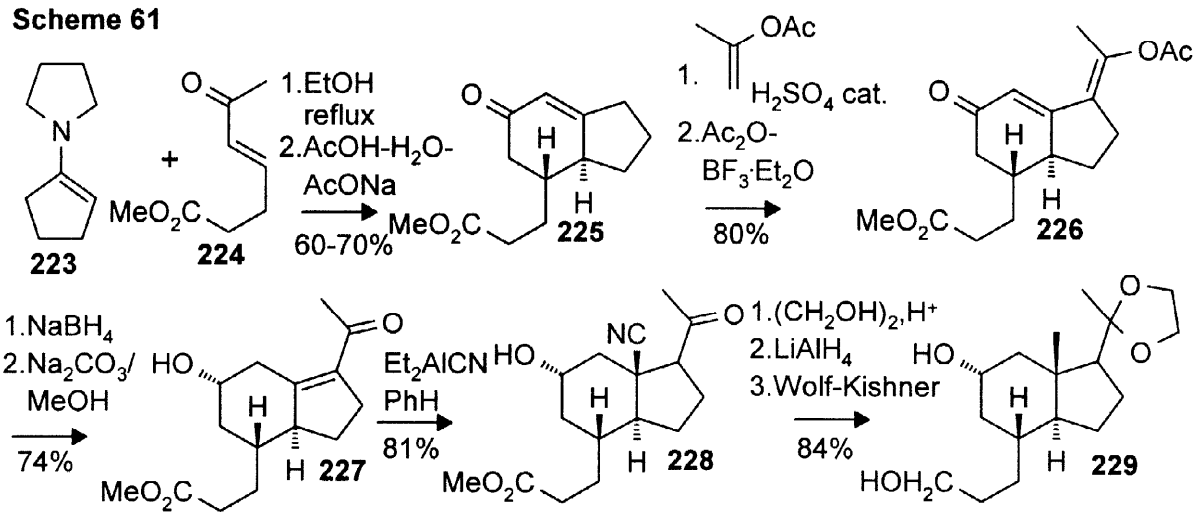


Scheme 60



Two Michael additions were used to generate *trans*-hydrindane system **221** in the enantioselective synthesis of estrone developed by Quinkert and coworkers.[181] Enolate **219** (Scheme 60) was reacted with α,β-unsaturated ketones **220a** and **b**. The yield and stereochemistry of the addition depended upon the nature of substituent R. With **220a**, R = H, rather disappointing results were obtained (see the scheme), however, using its trimethylsilyl analogue[98,174c,180,182] **220b**, a satisfactory yield of the adduct **221** was attained (no other product could be detected). Two synthetic routes to **222**, being a precursor of enolate **219**, were devised by those authors.

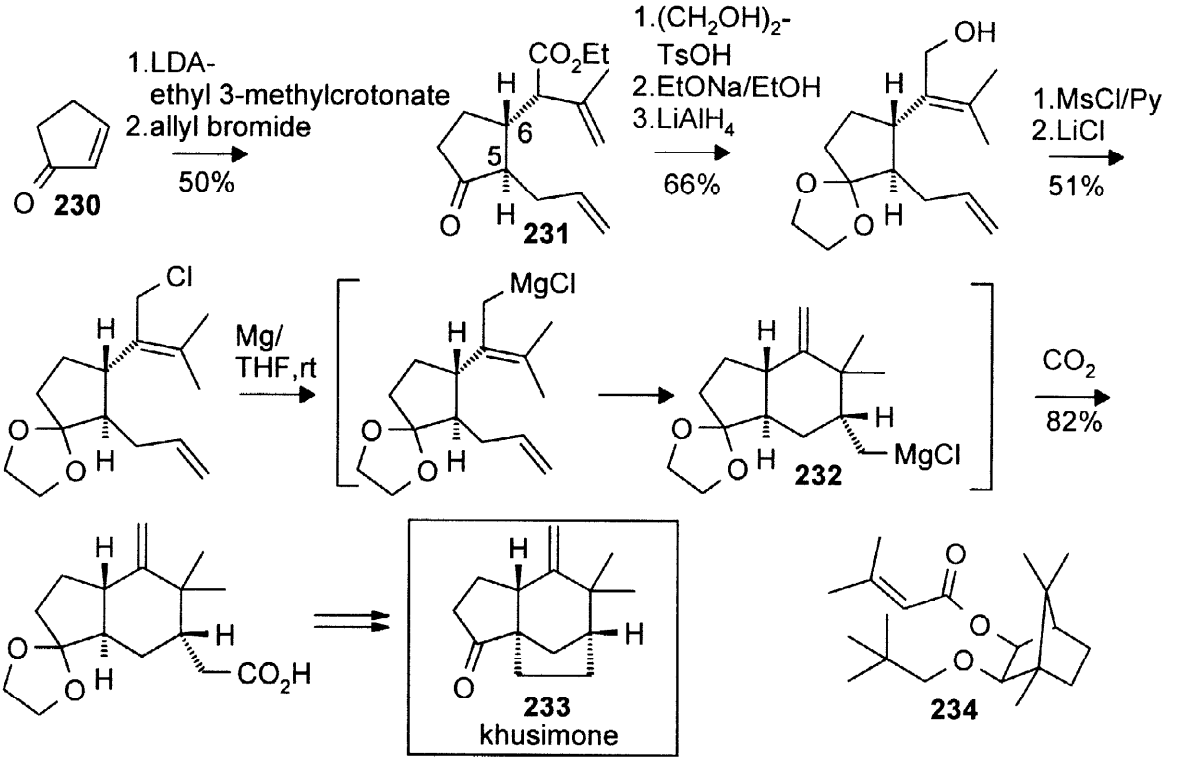
Scheme 61



Condensation of cyclopentanone enamine **223** (Scheme 61) and unsaturated ketone **224** followed by buffered hydrolysis of the rezultant imine group afforded[183] the bicyclic derivative **225**, which was converted to an enol acetate and then acylated in the γ-position with Ac_2O-BF_3·Et_2O to give **226**. After reduction of the keto group and

hydrolysis of enol acetate occurring with a simultaneous double bond migration, the α,β-unsaturated ketone **227** was treated with an excess of diethyl aluminum cyanide to give the *trans*-hydrindane derivative **228**. The authors failed to achieve conjugate addition of Me_2CuLi to **227** or to its derivative with the protected hydroxy group. However, the cyano group in **228** was efficiently reduced in a sequence of reactions involving protection of the keto group, reduction of the cyano group to an imine and further reduction of the imine (or the respective aldehyde) by the Wolf–Kishner method.

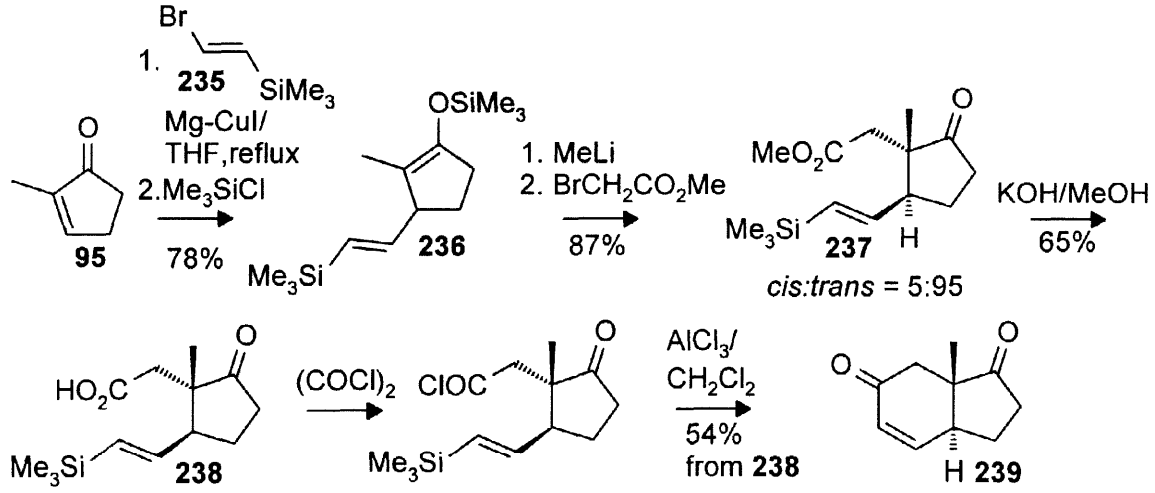
Scheme 62



Conjugate addition of an anion generated from ethyl 3-methylcrotonate to cyclopentenone **230** followed by enolate trapping with allyl bromide afforded[184] *trans*-substituted pentanone **231** (Scheme 62). Further transformation of this intermediate into racemic khusimone **233** involved carbometallation[185] and then carbonylation of the chloromagnesium derivative **232**. In the enantioselective version of this synthesis Oppolzer and coworkers[186] used camphor derived chiral crotanate **234**,[187] which leads to the initial adduct as a mixture of four diastereomers in a ratio of 48:5:9:9 (55% yield). The major component **231** with the required 5*S*,6*S* configuration (isolated yield 37%) was transformed into the natural product in an analogous way (after $LiAlH_4$ reduction step the chiral auxiliary was recovered).

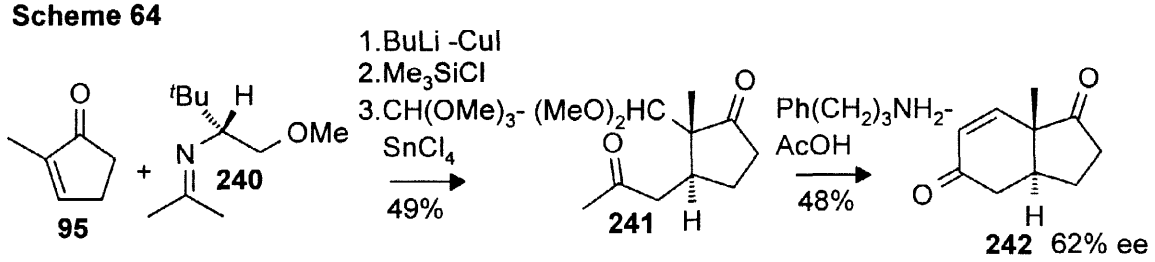
Independent but similar approaches to diketone **239** were published simultaneously by Denmark and Germanas,[188] and the Nakamura–Kuwajima group[189] Conjugate addition of vinylsilane reagent **235** to methylcyclopentenone followed by the trapping of the enolate with Me_3SiCl gave the *o*-trimethylsilyl derivative **236**, which was then treated with methyllithium and the resulting lithium enolate was alkylated with methyl bromoacetate. The intermediate **237** (Scheme 63 presents the first of these communications) with the required orientation of the substituents on the cyclopentane ring was obtained. The six-membered ring was closed using the vinylsilane acylation reaction. The ratio of *cis:trans* **239** was determined by one group as 5:95, but 10:90 by the other.

Scheme 63



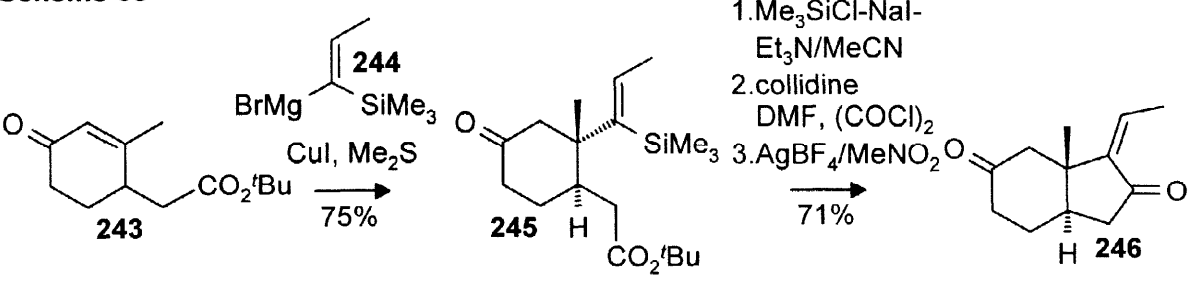
In an enantioselective approach[190] to dione **242** (Scheme 64) acetone enamine derived from (*R*)-*tert*-leucinol methyl ether **240** was treated first with BuLi and then with CuI to generate the respective lithiumcuprate which underwent conjugate addition to methylcyclopentenone. The resulting enolate was trapped with trimethylsilyl chloride. Silyl enol ether was then treated with trimethylorthoformate in the presence of $SnCl_4$ to give the masked aldehyde **241**. Cyclization of **241** was affected by 3-phenylpropyl amine and acetic acid. The final product was obtained in 24% overall yield, 62% ee.

Scheme 64



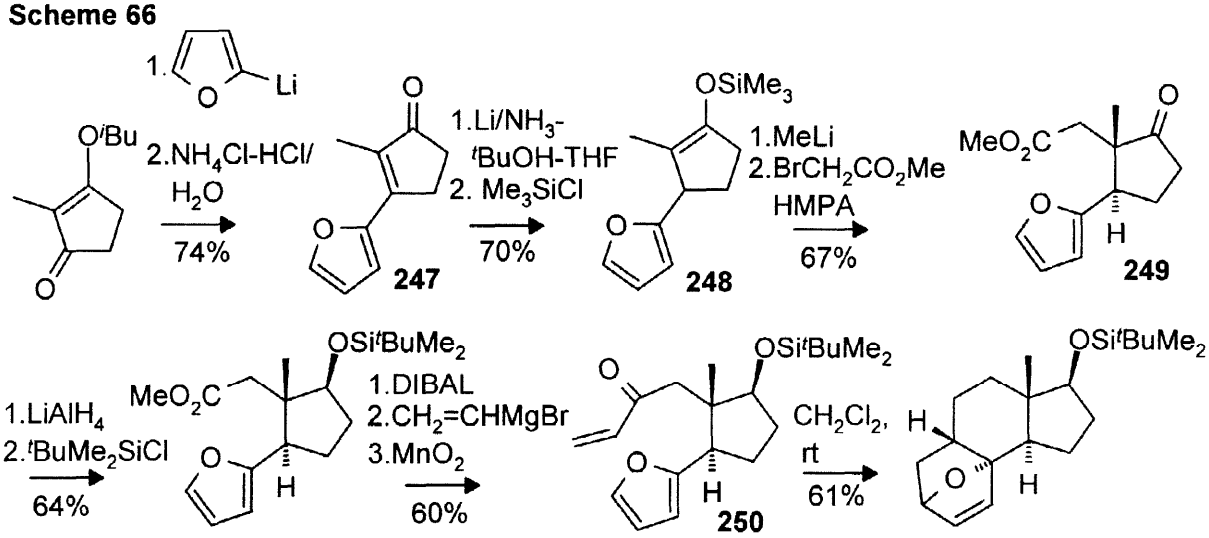
Cu-Catalysed addition of the Grignard reagent **244** to unsaturated ketone **243** (prepared from commercial 3-ethoxycyclohex-2-en-1-one in 81% yield) occurred with high stereoselectivity to give **245**.[189] After hydrolysis of the ester group of **245** and conversion of the resulting acid to the acid chloride, the cyclization was accomplished with $AgBF_4$ in nitromethane to give **246** (97% pure). Interestingly, it was mentioned that the Grignard reagent prepared from (*Z*)-(1-bromo-1-trimethylsilyl)-prop-1-ene failed to react with **243**. However, a few years later the same authors[191] reported that in the Me_3SiCl-mediated addition[192] of $Me_2C{=}CHMgBr$ to enone **243** (in the presence of $CuBr{\cdot}Me_2S$) gave the respective adduct in 78% yield. The product obtained in this way has been used in cortisone synthesis.

Scheme 65



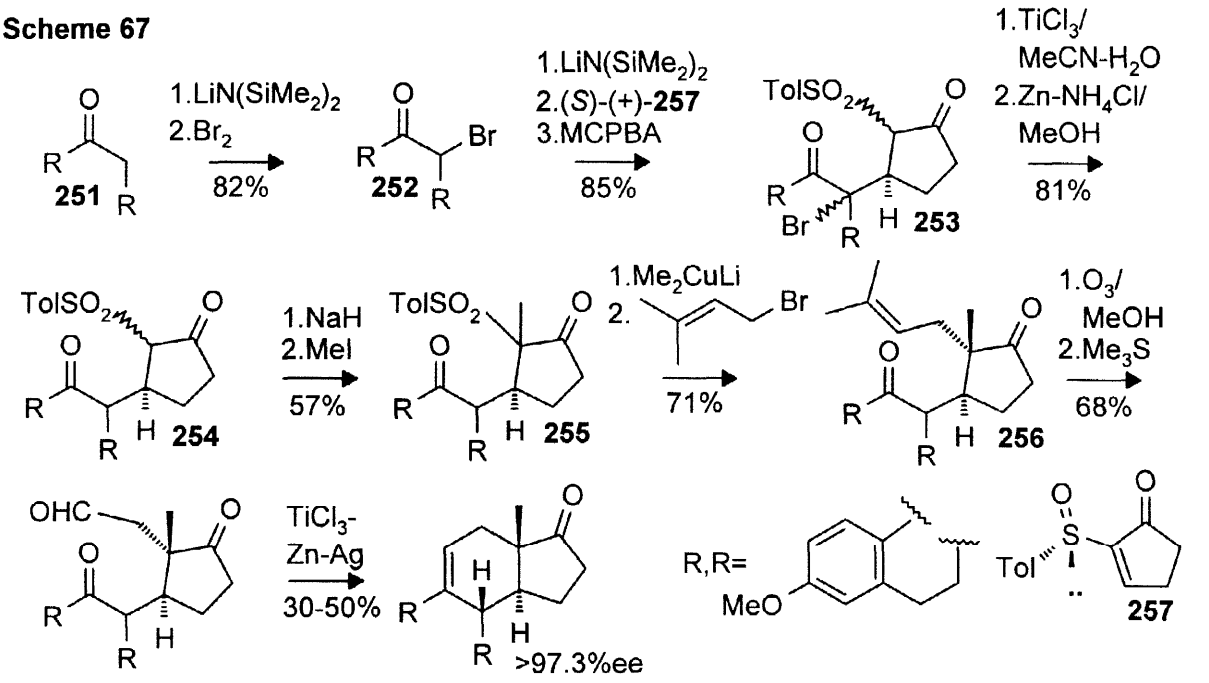
De Clercq and coworkers[193-196] have developed a steroid synthesis involving an intramolecular Dieles–Alder reaction of furan and suitable dienophilic moieties, for example **250** (Scheme 66). With respect to stereochemistry, this approach makes use of stereoselective alkylation of the lithium enolate generated from **247**, with methyl bromo acetate (**248** →**249**, Scheme 66).

Scheme 66



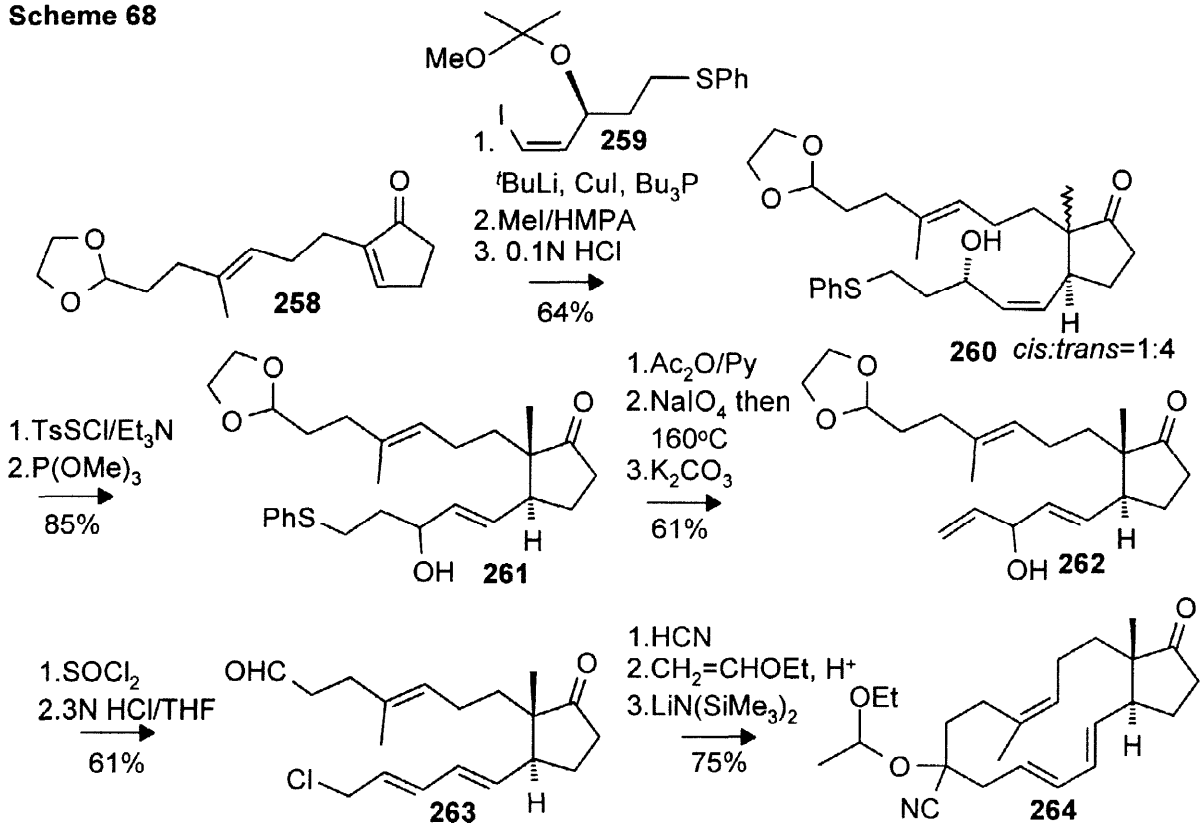
In the enantioselective estrone synthesis developed by Posner and coworkers[197] crucial steps consist of Michael addition of the bromoenolate generated from **252** to optically active cyclopentenyl sulfoxide **257**. The adduct was oxidized to the corresponding sulfone **253**. It has been determined that the this product was formed with high enantioselectivity with respect to the chiral centre at C_{14} (>97% ee). The addition of the enolate generated directly from ketone **251** to **257** gave much lower optical induction. Bromoketone **253** was reduced with Zn-NH_4Cl in methanol. The ketosulfone **254** was regioselectively methylated at C_{13} and the product **255** was subjected to reductive cleavage of the tosyl group and allylation, which provided intermediate **256** diastereoselectively. Transformation of **256** into the final product involves ozonolysis and McMurry coupling.[198,199]

Scheme 67



In the synthesis[200] of triene **264** (Scheme 68), required for the study of intramolecular Diels–Alder reaction, conjugate ketone **258** was submitted to the Michael addition-enolate trapping procedure[201] using cuprate derived from vinyl iodide **259** and then methyl iodide and a mixture of 14α-H products **260**, with the *cis:trans* ratio 1:4, was obtained. This product was subjected to the double bond isomerisation[202] to give **261** and then the terminal double bond was introduced *via* sulfoxide elimination. Transformation of alcohol **262** into chloride **263** involved an allylic rearrangement. The macrocycle was closed by the protected cyanohydrin alkylation method. The respective diketone, prepared by hydrolysis of the cyanohydrin ether **264**, underwent intramolecular cyclization to give 5β-androst-6-en-3,17-dione in an excellent yield.

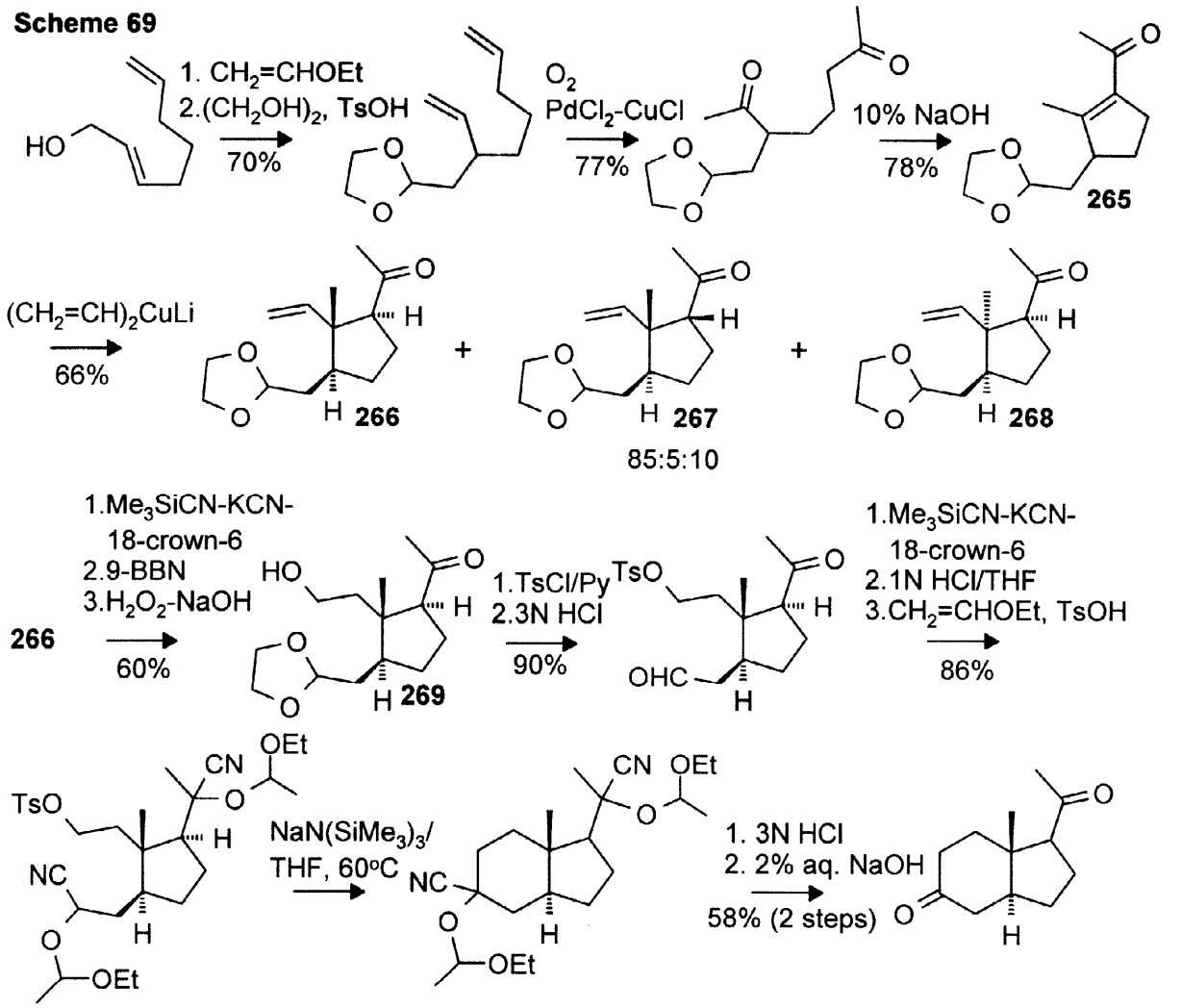
Scheme 68



Addition of vinylcuprate to enone **265**, prepared as shown in Scheme 69, proceeded mainly from the opposite side to the substituent at latent C_{14} to afford[203] the precursors of *cis*-(**268**) and *trans*-(**266** and **267**) hydrindanes in a ratio of 1:9. The ketone carbonyl group in the main product **266** was protected as a cyanohydrin derivative whereupon hydroboration-oxidation were carried out to give, after deprotection of the carbonyl group, primary alcohol **269**. The ring C closure was achieved using the reaction of an anion generated from ethyoxyethyl cyanohydrin with the tosyloxy group .

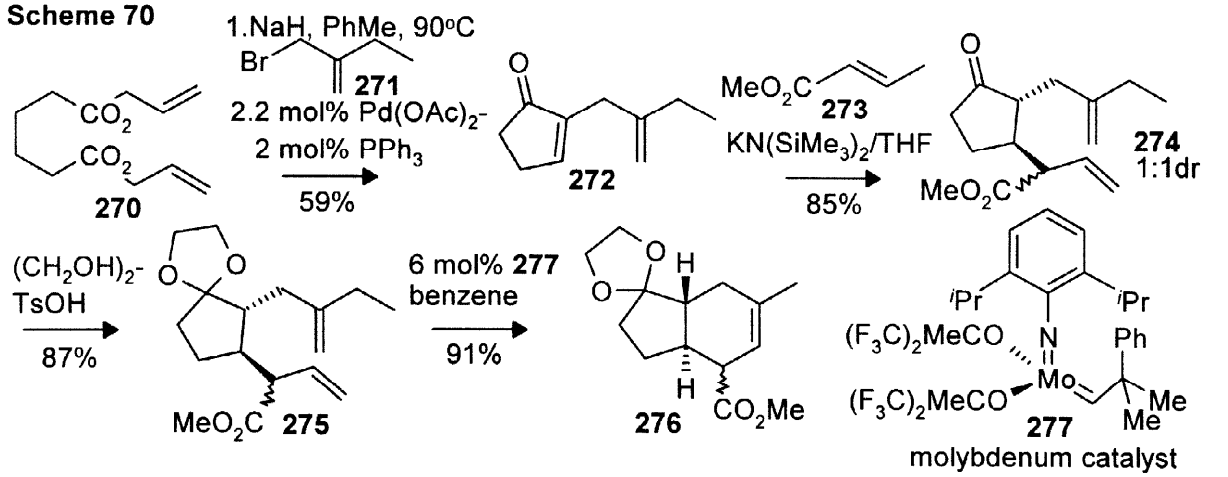
Olefin metathesis has been successfully applied[204] to a six-membered ring closure in the course of coronafacic acid synthesis (Scheme 70). Diallyl adipate **270** was transformed into cyclopentenone **272** by Dieckmann condensation followed by 2-carboallyloxy cyclopentanone alkylation with 2-ethyl allyl bromide **271** and palladium catalysed elimination of allylcarboxy group.[205] Michael addition of methyl crotonate **273** anion (cf. Scheme 62) yielded *trans*-adduct **274** as a mixture of diastereomers differing in the carbomethoxy group orientation. The addition was apparently selective with respect to the chiral centres in the cyclopentane ring. The oxo group in **274** was protected as the ethylene ketal **275**, which was treated with the molybdenum catalyst **277**[206,207] in benzene at

Scheme 69



room temperature to give hydrindane derivative **276** in an excellent yield.[208] Ring closing metathesis of free ketone **274** was not efficient. A rhodium catalyst used in some other olefin metathesis reactions was also effective. The cyclization product **276** was further transformed into the target natural product.

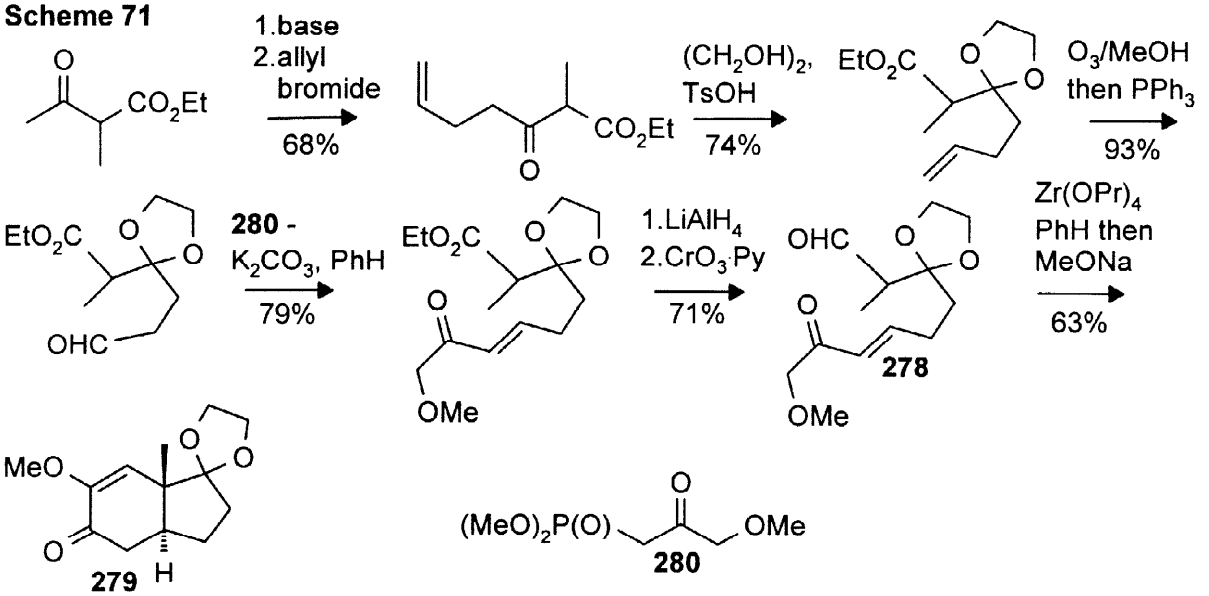
Scheme 70



5.2. Intramolecular conjugate additions, alkylations and related reactions

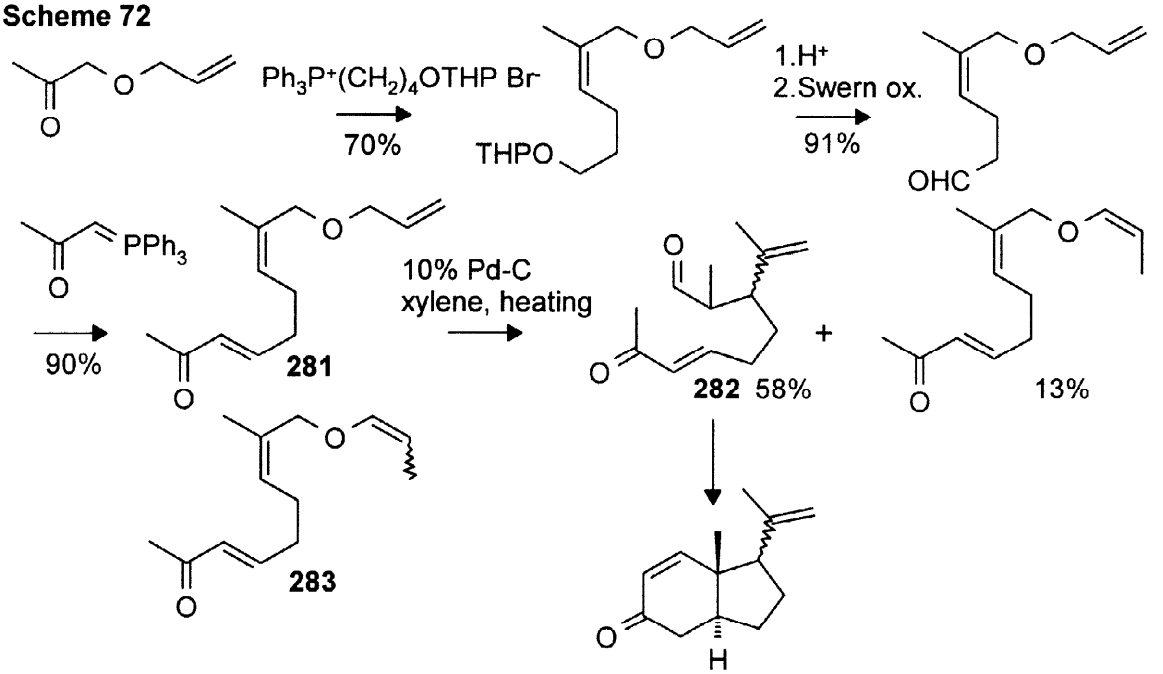
Stork and coworkers[209,210] have developed a method for the synthesis of *trans*-hydrindane building block **279** for corticosteroid synthesis (Scheme 71). Zirconium tetrapropoxide-mediated cyclization of **278** followed by the aldol condensation yielded **279** with high stereoselectively (*cis:trans* ratio 1:25).

Scheme 71



The starting material for the $Zr(OPr)_4$-catalysed cyclization has also been prepared along a shorter route, as shown in Scheme 72. The Claisen-type rearrangement of **281** was achieved by heating with 10% palladium-on-carbon. The reaction proceeds most likely *via* a vinyl ether intermediate **283**. Interestingly, it was noted that cyclization of the propenyl derivative **282** was less selective than that of the above-described ketal **278**.

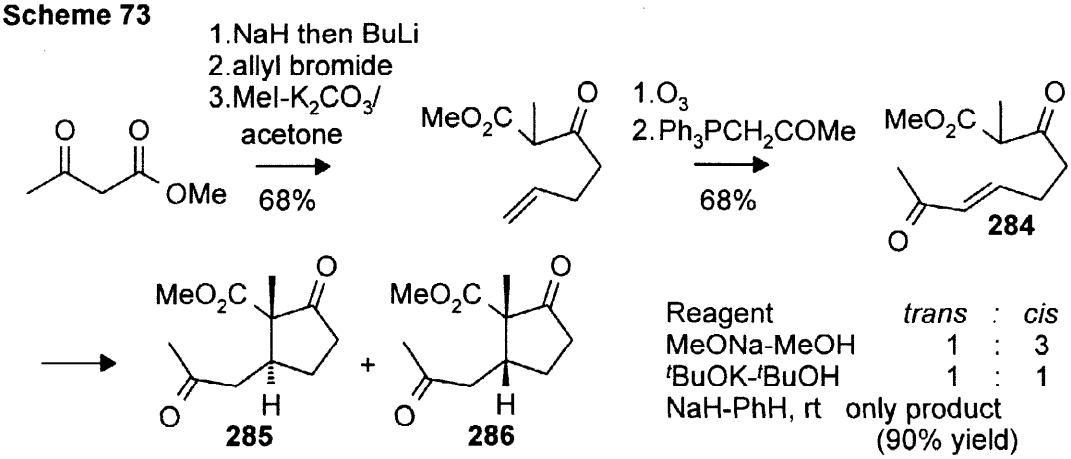
Scheme 72



Sequential alkylation of dianion of acetylacetate with allyl bromide and methyl iodide followed by the ozonolysis and Wittig reaction afforded[211] **284** another acyclic precursor of hydrindane rings (Scheme 73). It has

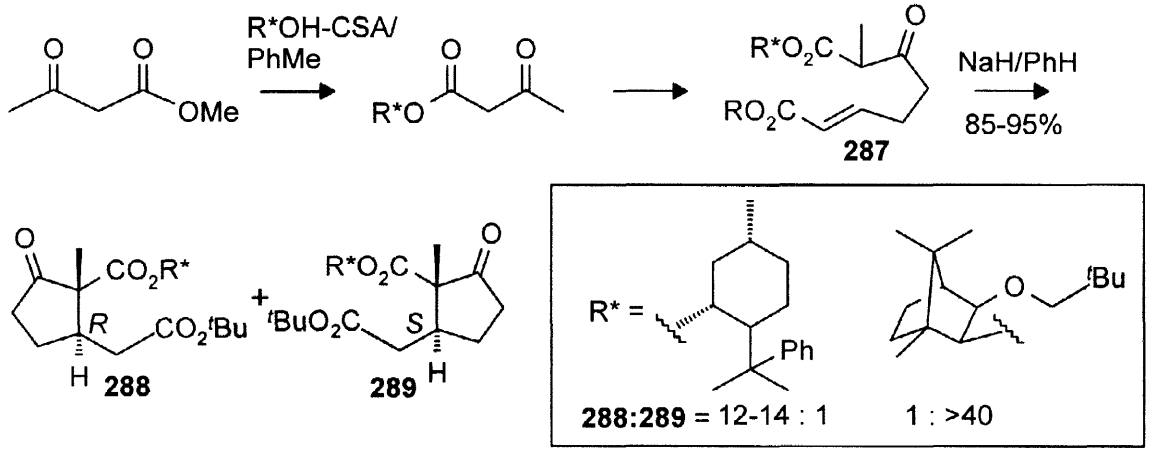
been found that cyclization of **284** with sodium hydride in benzene at room temperature affords exclusively *trans*-product **285** presumably *via* chelated anionic intermediate. Cyclization in protic media resulted in a mixture of diastereomers **285** and **286**.

Scheme 73



Asymmetric induction in the above-discussed intramolecular conjugate addition by a chiral auxiliary has been studied.[212] Cyclization of ester **287** where R*= 8-phenylmenthyl[213] or neopentyloxyborynyl[214]gave very promising results with the diastereomer ratio **288**:**289** in the range 12:1 - 14:1 and 1:40 (see Scheme 74).

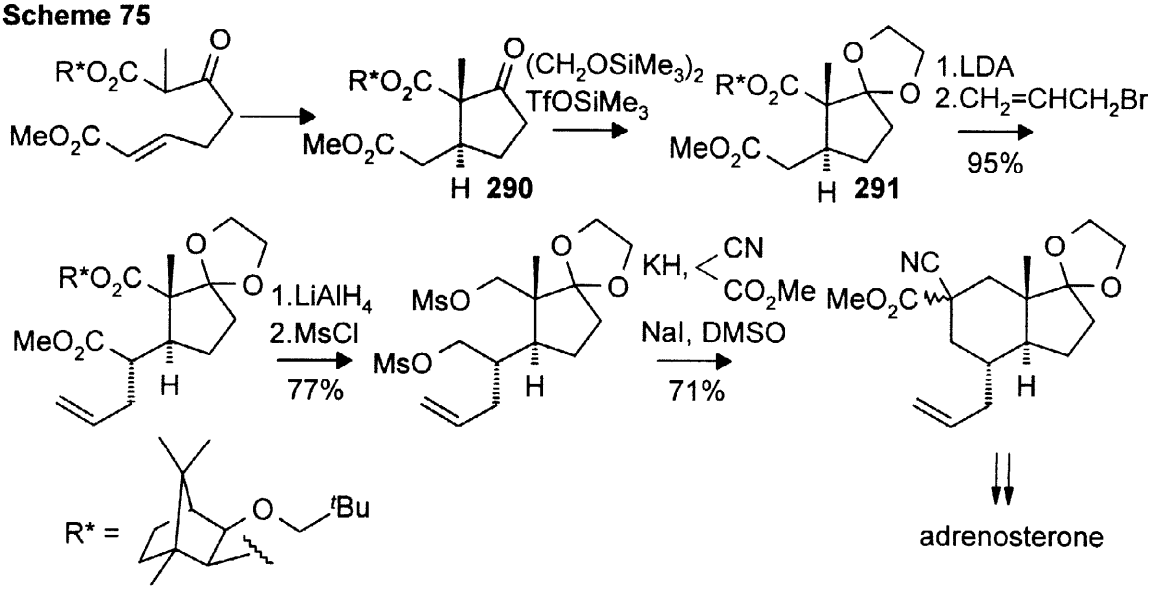
Scheme 74



This method was later applied to a synthesis of the CD fragment of adrenosterone, as shown in Scheme 75.[215] The product of the cyclization, **290**, bearing the norbornane derived auxiliary, was transformed into dioxolane **291** by the method of Noyori and coworkers.[216] Alkylation of **291** with allyl bromide was highly stereoselective. The six-membered ring closure was achieved with the aid of methyl cyanoacetate.

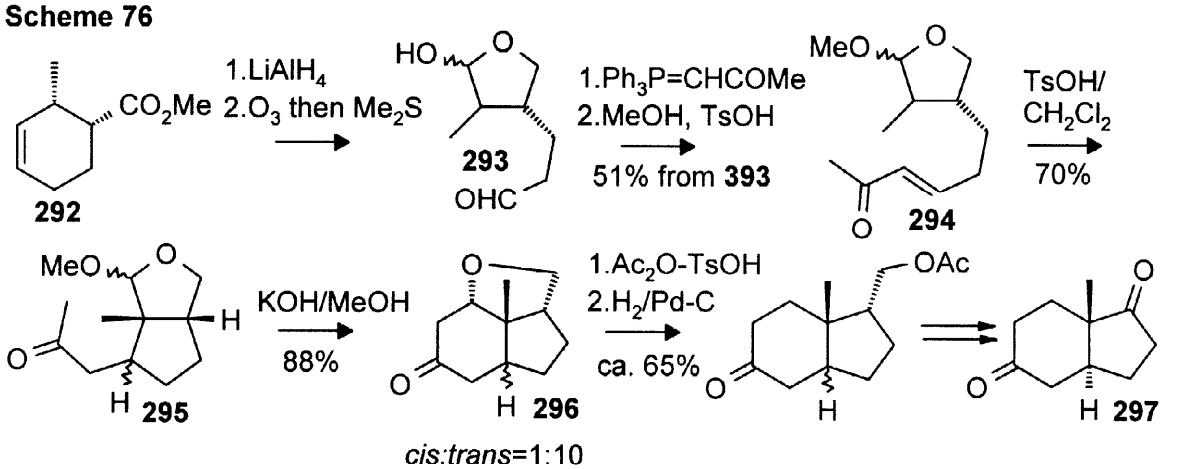
The synthesis of *trans*-hydrindanone **297** (Scheme 76) from easily accessible 3-methyl-4-carboxycyclohexene **292** involves partly protected dialdehyde **293** and unsaturated ketone **294**,[217] which upon treatment with an acid underwent cyclization (*via* its dihydrofuran derivative) to give *cis*-bicyclic oxa intermediate **295** with the required stereochemical arrangement around the cyclopropane ring. Aldol condensation provided tricyclic product **296**, mainly the *trans*-isomer (*cis*:*trans* = 1:10), which was then transformed into diketone **297**. It has been shown that the analogous transformation of the optically active unsaturated ketone **292** (obtained starting from the Diels–Alder

Scheme 75



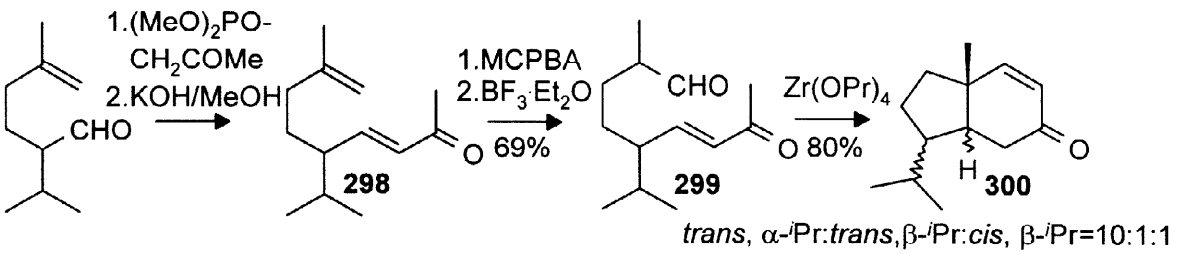
reaction of *trans*-piperylene and (–)-β-pinenyl acrylate) occurs without loss of optical activity. This method offers a unique approach to hydrindane derivatives with the α-oriented carbon substituent at C_{17}, and may be used in vitamin D and sterol analogue syntheses.

Scheme 76



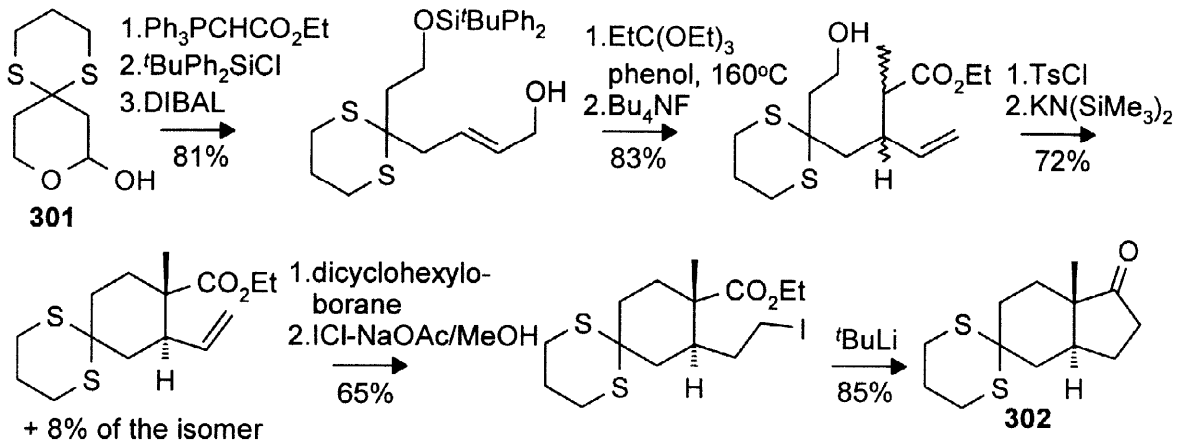
Tandem Michael-aldol reaction was used to prepare isopropylhydrindanone **300**, which served as an intermediate in the synthesis of retigeranic acid.[218] Epoxydation of **298** and rearrangment of the epoxide gave aldehyde **299** (Scheme 77), which upon treatment with zirconium tetrapropoxide afforded a mixture of three products **300** (80% combined yield) with (1) *trans*-ring junction and the α-oriented isopropyl group, (2) *trans*, β-isopropyl and (3) *cis*, β-isopropyl, in a ratio of 10:1:1, respectively.[219]

Scheme 77



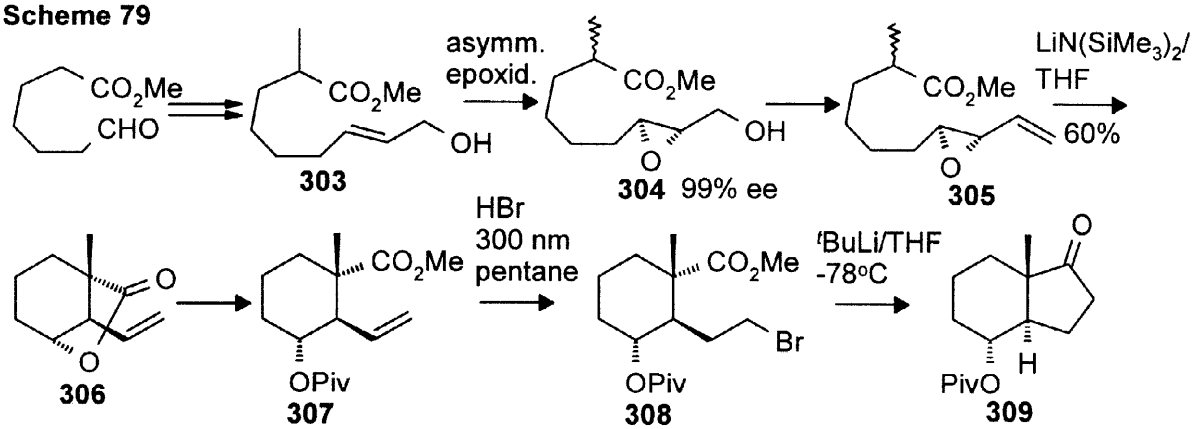
Claisen rearrangement and intramolecular ester alkylation have been used[220,221] as the key steps in the synthesis of mono-protected dione **302** from easily accessible dithiane derivative **301** (Scheme 78). The synthesis involved 10 steps and afforded the product in 27% overall yield.

Scheme 78



The Katsuki–Sharpless epoxidation and stereoselective alkylation of allyl epoxide[222] have been used[223] in the synthesis of *trans*-hyndrindane **309** shown in Scheme 79. Epoxidation of alcohol **303** afforded product **304** with high selectivity. Swern oxidation of the hydroxy group in **304** followed by the Wittig reaction afforded the key intermediate **305**. The treatment of **305** with $LiN(SiMe_3)_2$ resulted in regio- and stereoselective formation of a new C-C bond and adjustment of the chiral centre in α-position to the carbonyl group. Additionally, intramolecular *trans* esterification occurred to give the bicyclic product **306**. Further transformations of **306** invokes photochemical addition of HBr to the double bond of **307** to give **308** and cyclization initiated by halogen-metal exchange. Detailed reactions conditions and yields were not reported.

Scheme 79



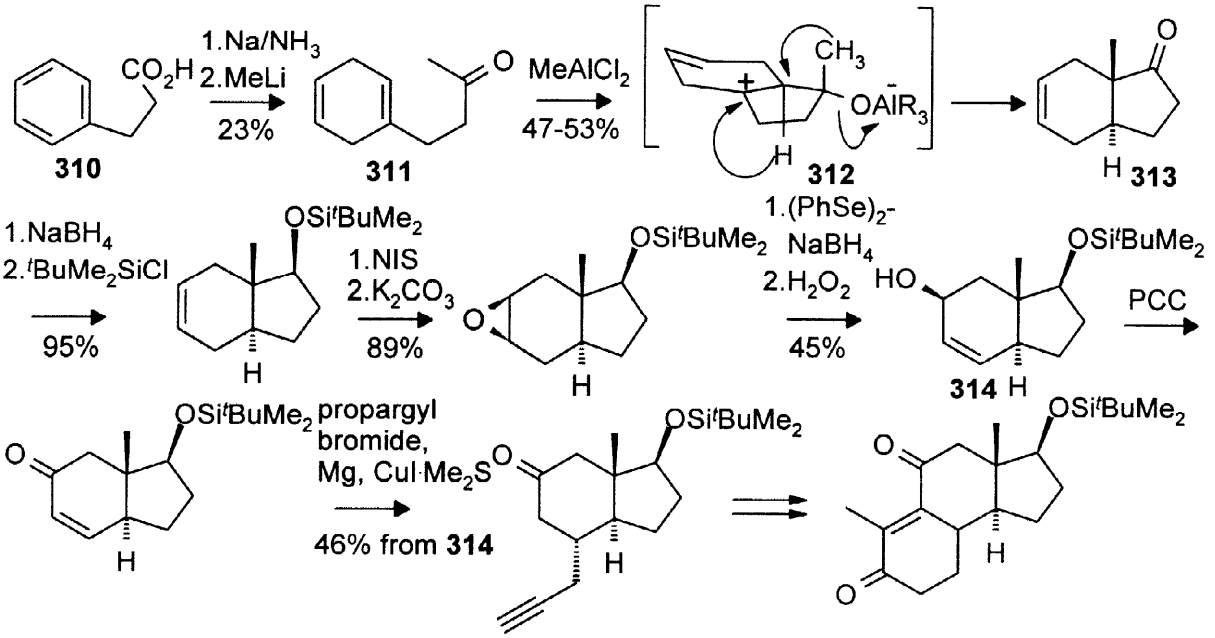
6. Carbocationic Cyclizations

6.1. Lewis acid promoted cyclizations and related processes

An approach to *trans*-hydrindane systems, based upon the ene reaction,[224] commenced from hydrocinnamic acid **310** (Scheme 80), which was subjected to the Birch reduction followed by treatment of the crude product with methyl lithium. Thus obtained dienone **311** was heated with $MeAlCl_2$ (in CH_2Cl_2, 90 °C, a sealed tube) to give **313** as the only product. The authors suggested that the first step of the reaction is reversible with the intermediate **312**

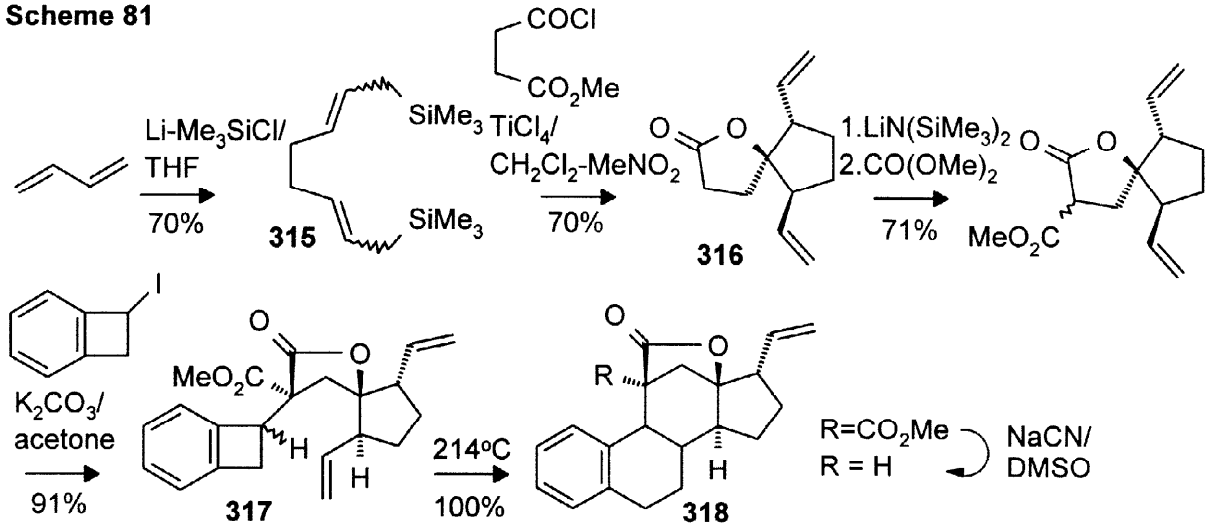
energetically preferred over its *cis* counterpart owing to the equatorial orientation of the bulky alkoxy group. The relevant mechanistic studies[225] have shown that the hydride anion and methyl group shifts are not concerted.[226] The hydrindane derivative **313** was used in the steroid synthesis as outlined in Scheme 80.

Scheme 80



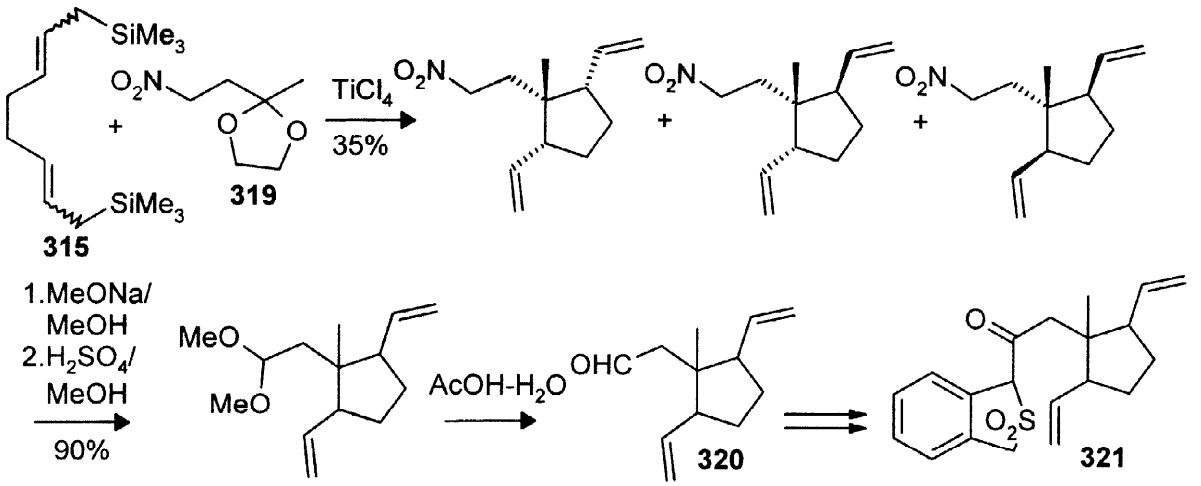
An interesting $TiCl_4$-mediated dialkylation of various electrophiles with 1,8-bis(trimethylsilyl)octa-2,6-diene **315** (Scheme 81), which was prepared in one step from butadiene and trimethylsilyl chloride, has been developed by Santelli and coworkers.[227] Thus, $TiCl_4$-mediated reaction of **315** with carboethoxypropionyl chloride afforded lactone **316** as the major diastereomer (*dl*:*meso* = 11.5:1). Methoxycarbonylation of **316** followed by alkylation with iodobenzocyclobutane gave the Diels–Alder intermediate **317** (direct alkylation of ester **316** with iodobenzocyclobutane failed). The heating of **317** provided isomerically pure estrone derivative **318**.

Scheme 81



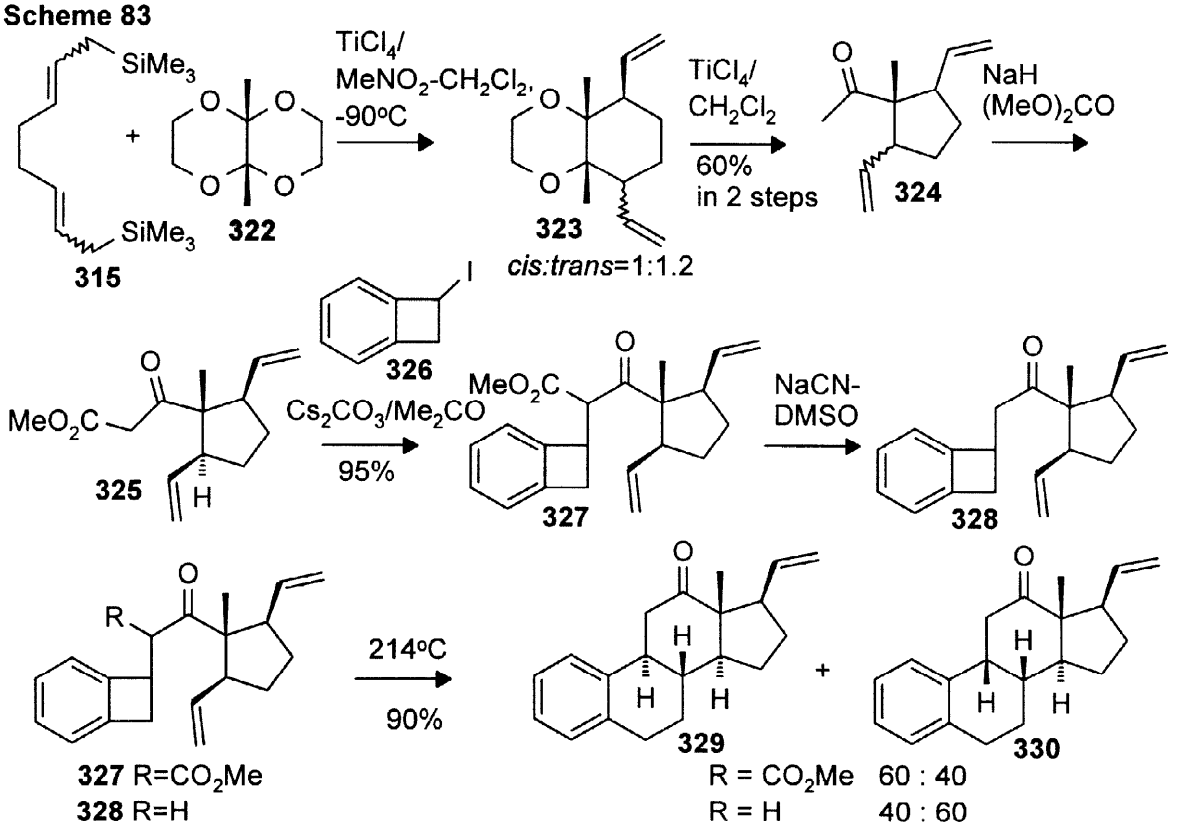
Likewise, the reaction of **315** (Scheme 82) with nitro acetal **319** gave an inseparable mixture of three isomeric cyclopentane derivatives, [228] which were subjected to the Nef reaction and then the resulting aldehyde derivative **320** was transformed into the estrane precursor **321**.

Scheme 82



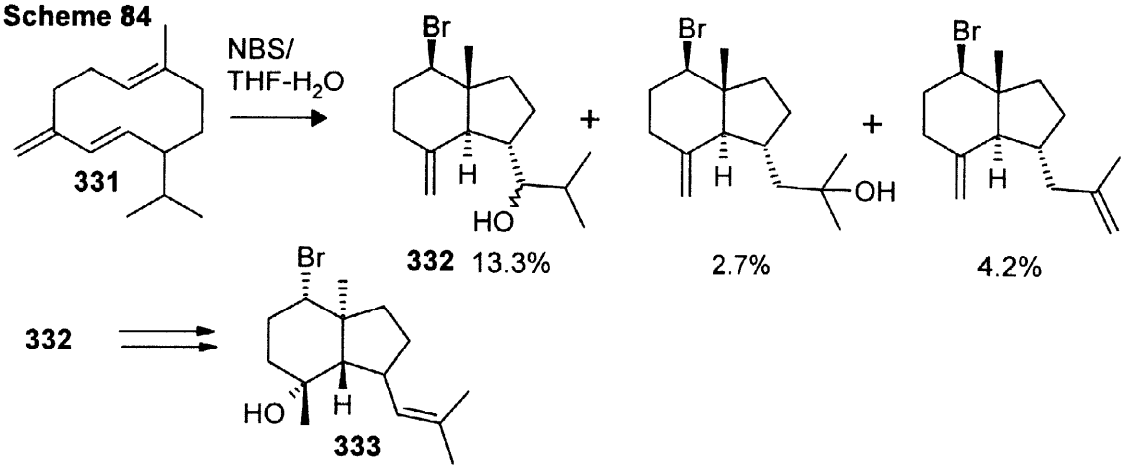
In the more advanced version of this approach to *trans*-hydrindane systems[229,230] bis-diallylsilane **315** was reacted with α-diketone diketal **322** in the presence of $TiCl_4$ to give the substitution product **323** as a mixture of diastereomers differing in the relative orientation of the vinyl groups (Scheme 83). These isomers upon treatment with $TiCl_4$ underwent a pinacol rearrangement to give the oxo-derivatives **324**. After separation, the *cis*-isomer was carbomethoxylated and then the keto ester **325** was coupled with iodobenzocyclobutene **326**. The carbomethoxy group could be efficiently removed from that product by the Krapcho process. Thermolysis of compounds **327** and **328** afforded the respective estrane derivatives as mixtures of isomers. Thus, the keto ester **327** (R = CO_2Me) after *in situ* decarbomethoxylation gave a mixture of *trans-anti-cis* and *cis-anti-cis* products **329** and **330** in a ratio of 60:40 whereas the ketone **328** (R = H) gave **329** and **330** in a ratio of 40 : 60.

Scheme 83



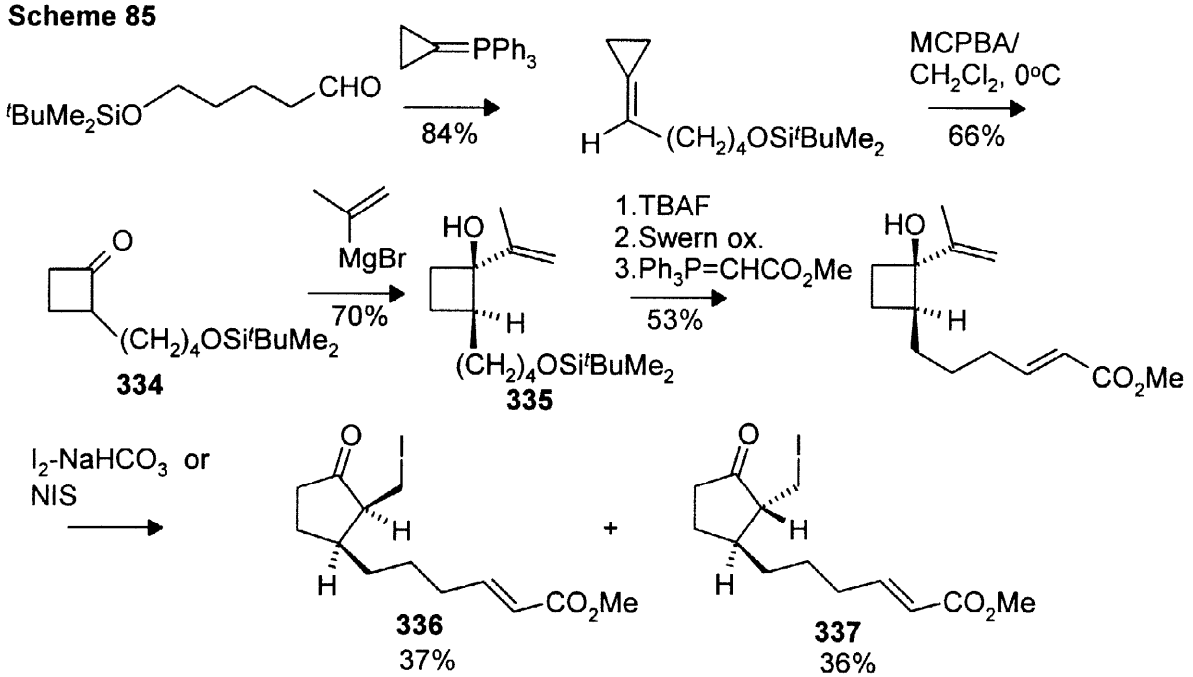
trans-Annular cyclization with *iso*-propyl group migration occurred[231] when (–)-germacrene **331** (Scheme 84) was treated with *N*-bromosuccinimide (NBS) in aqueous THF. Several bicyclic bromo hydrindanes and decalins were obtained. One of the major products **332** was transformed into racemic oppositol (**333**).

Scheme 84



The iodonium ion induced rearrangement of vinylcyclobutanol derivatives has been applied for preparation of disubstituted cyclopentanones that may be useful in the synthesis of hydrindane derivatives.[232,233] In a typical example, easily accessible cyclobutanone **334** (Scheme 85) was transformed into allylic alcohol **335**, which, after appropriate adjustment of the side chain, was treated with iodine - $NaHCO_3$ or N-iodosuccinimide. Iodination and ring enlargement occurred to give a mixture of diastereomeric iodomethyl cyclopentanones **336** and **337**.

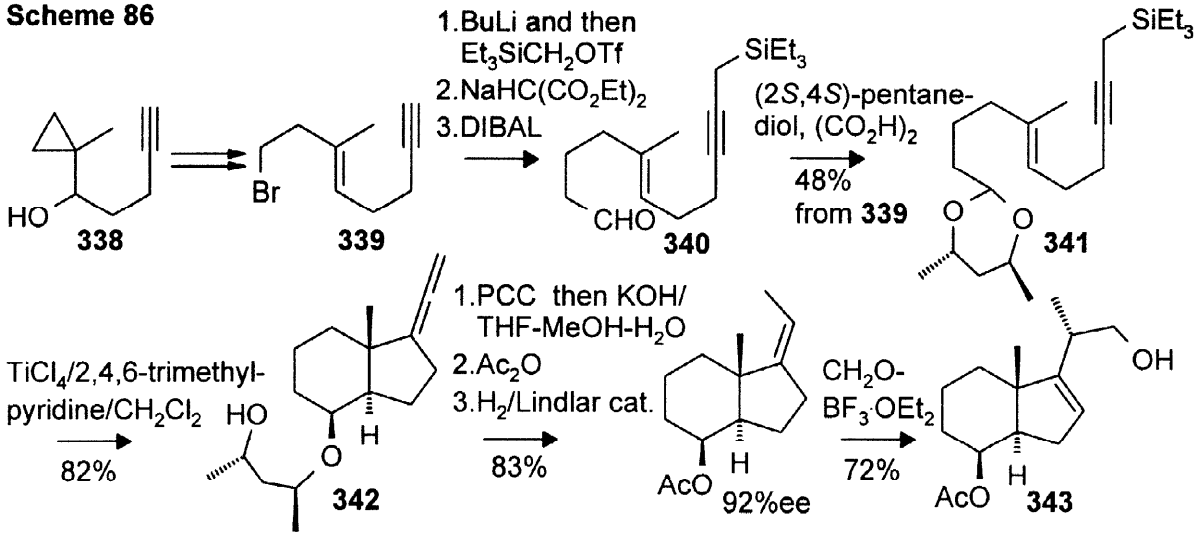
Scheme 85



6.2. Polyene cyclizations and related processes

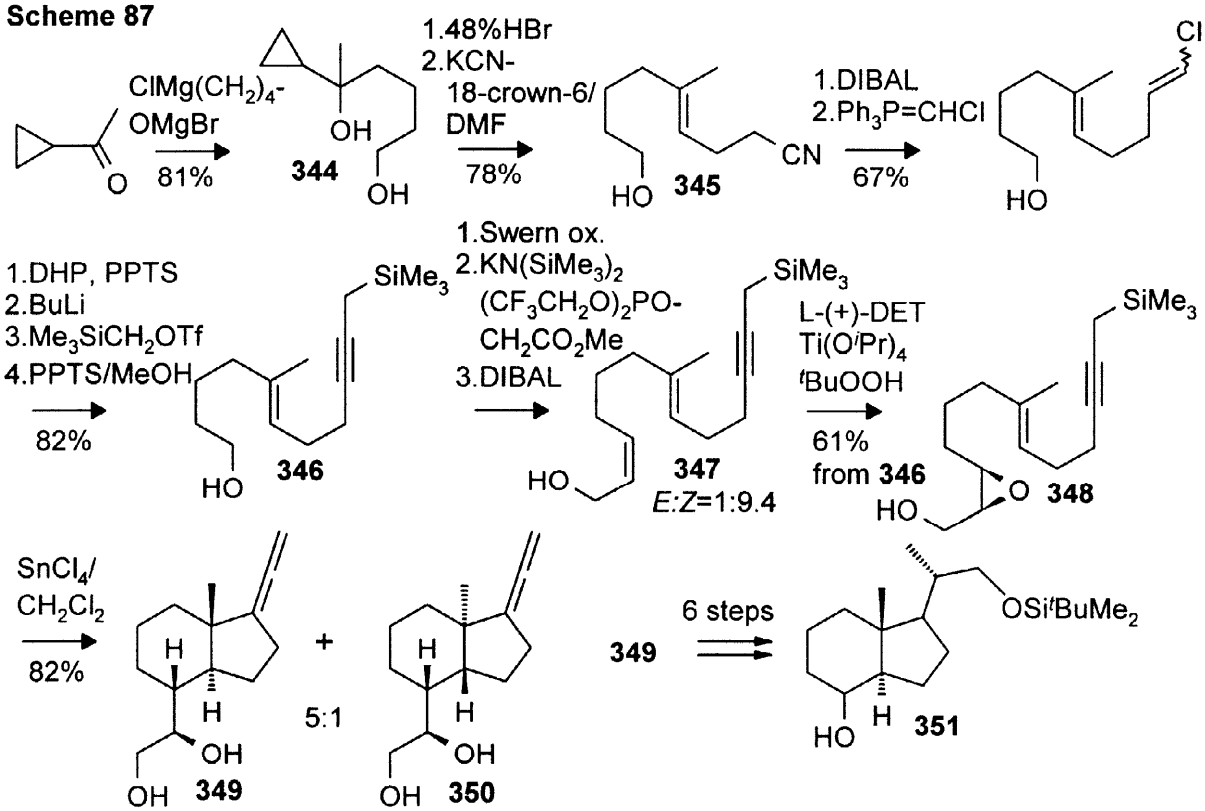
Polyene cyclizations pioneered by W. S. Jonhson, van Tamelen and E. J. Corey provided a method for the simultaneous formation of several carbon-carbon bonds in one reaction, and thereby made possible a relatively short and efficient route to many polycyclic natural products. This topic has been extensively reviewed.[234] The present report is confined to one or two "classic" applications and to some important recent methodological contributions.

Scheme 86



For the synthesis of vitamin D hydrindane rings[235] **343** the cyclopropane derivative **338** (Scheme 86) was rearranged into homoallylic bromide **339** using the modified Julia procedure.[236,237] Homologated aldehyde **340** was transformed into the optically active ketal **341**, which was subjected to biomimetic acid-catalysed cyclization. The product consisted of *trans*-hydrindane **342** and its 13α-Me, 14β-H isomer (not shown) in a ratio of 87:13. The required product **342** was isolated in 82% yield. Further transformations of the intermediate **342** involve ene reaction with formaldehyde.[238] A high degree of chirality transfer in this synthesis is of particular interest.

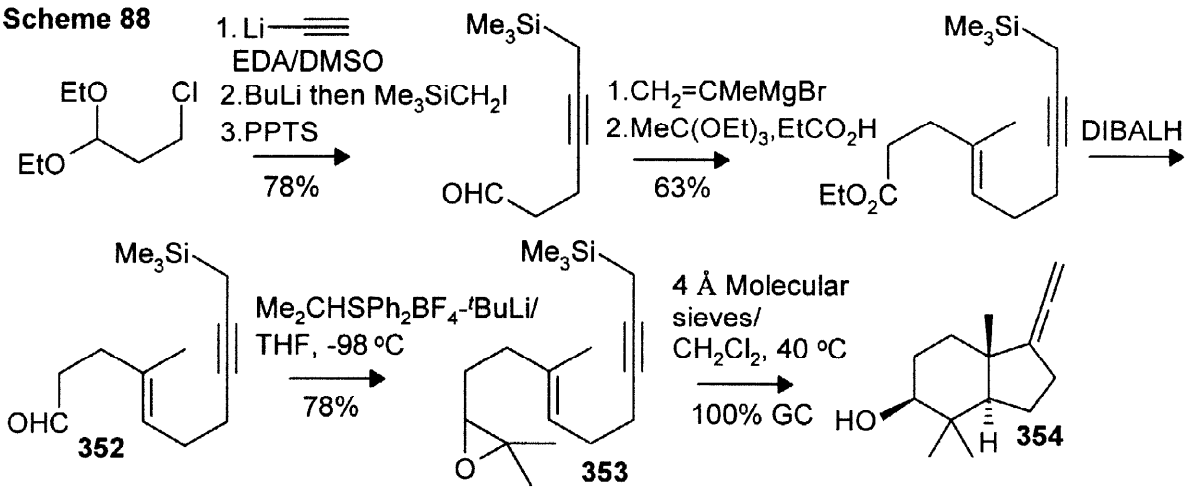
Scheme 87



Another approach to the vitamin D hydrindane system[239] is presented in Scheme 87. The cyclopropyl diol **344** was transformed into the intermediate allylic bromide using the Julia method[236] and then into cyanide **345**.

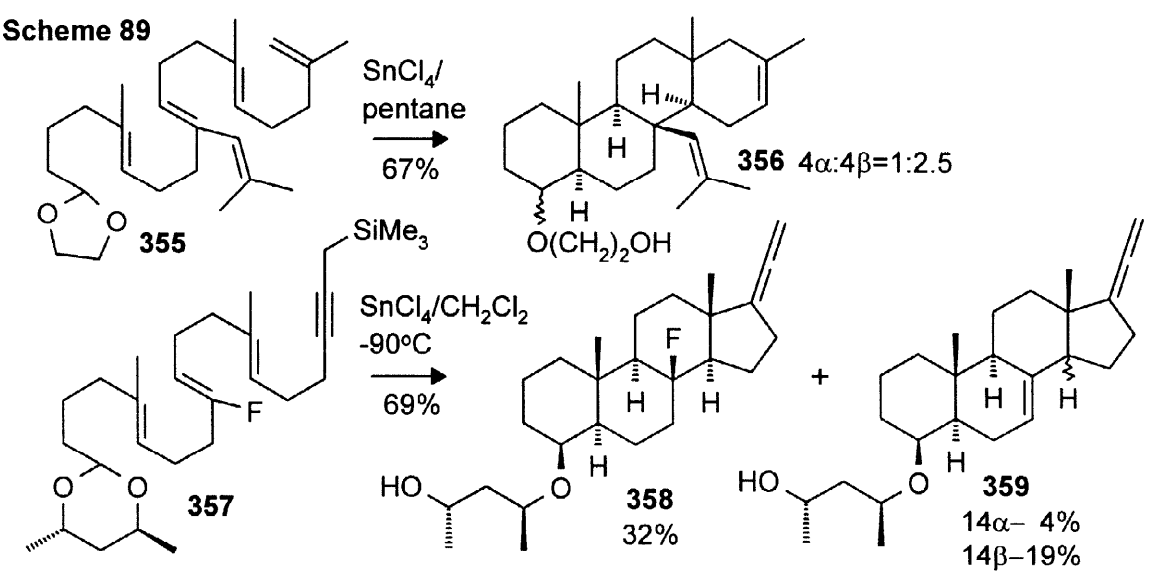
Construction of the acetylene moiety involved: (1) reduction of **345** to the corresponding aldehyde; (2) addition of the chlorine containing Wittig reagent; (3) elimination of HCl from vinyl chloride; and (4) addition of trimethylsilylmethanol triflate. Further elaboration of **346** consisted of oxidation of the hydroxy group and reaction of the aldehyde with the Still and Gennari reagent[240] followed by reduction of the ester group. Allylic alcohol **347** was subjected to asymmetric epoxidation. The epoxide **348** (ca. 90% ee) was treated with $SnCl_4/CH_2Cl_2$ at -95 °C to afford the required intermediate **349** and its diastereomer in a ratio of 5:1. Compound **349** was further transformed into the vitamin D precursor **351** by well known methods (see Scheme 86). Cyclization of the epoxide differing from **348** in *trans* orientation of the substituents at the oxirane ring also afforded the corresponding hydrindane derivatives, however, stereoselectivity of cyclization obtained by this route was markedly lower (2.4:1).

Scheme 88



It has been shown recently that a zeolite may serve as a catalyst in cyclization of epoxide-containing polyenes.[241] Treatment of **353** (Scheme 88) with 4 Å molecular sieves in CH_2Cl_2 or $CHCl_3$ at reflux temperature afforded the bicyclic product **354** quantitatively. The reaction was studied with respect to solvent, water content in the catalyst, and the possible side products. The use of diphenylisopropylsulphonium tetrafluoroborate[242] to generate epoxide **353** from the intermediate aldehyde **352** is noteworthy.

Scheme 89



Considerable progress has been made recently in asymmetric synthesis of steroids by the Johnsons cyclization

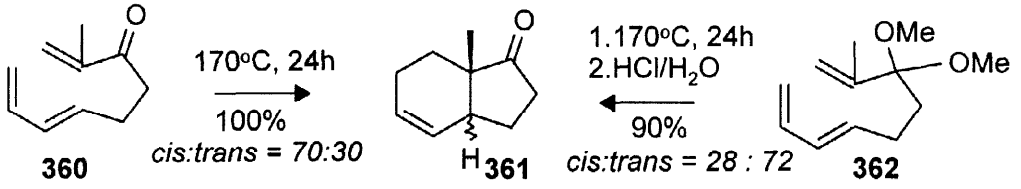
with different cation-stabilizing auxiliaries. For example, tetracyclization of substrate **355** (Scheme 89) with the acetal initiator and cation-stabilizing isobutenyl group afforded **356** (4α:4β=1:2.5) in 67% yield accompanied with D-ring double bond position isomers. The combined yield of tetracyclic products exceeded 75%.[243] The substrate **357** with the chiral acetal unit and fluorine as the cation-stabilizing auxiliary and the propargylsilane terminator afforded tetracyclic products in the combined yield of 69%, the main products being the 14α-H fluoro **358** and 14β-H 7-dehydro **359** pregnane derivatives.[244]

7. Intramolecular cycloadditions and electrocyclic rearrangements

7.1. Intramolecular Diels–Alder reaction

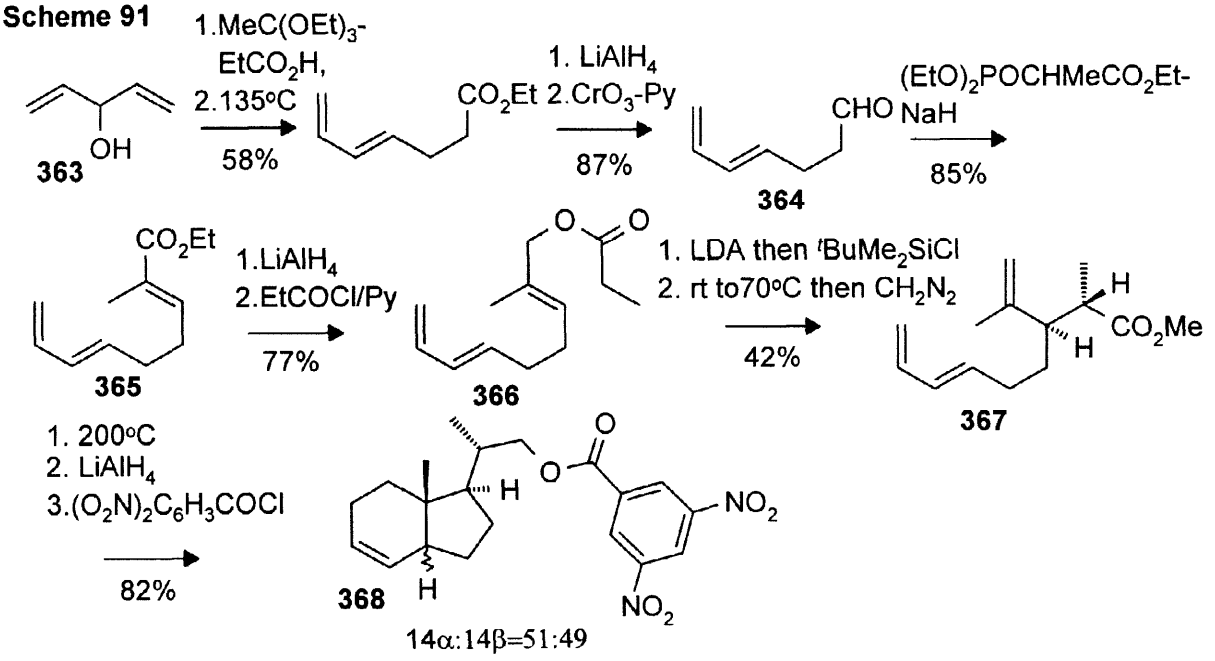
Comprehensive reviews on the intramolecular Diels–Alder reaction have been published.[245] In a work involving the *trans*-hydrindane rings construction by intramolecular [4+2] cycloaddition an interesting dependence of the cycloaddition stereochemistry upon the substituent at the latent C_{17} in the triene was noted. [246] While the trienoic ketone **360** (Scheme 90) afforded mainly the *cis*-hydrindene derivative **361**[247] its ketal derivative **362** provided mainly the *trans*-product. Similar effect was also observed when thio-analogues of **362** was used.[248,249]

Scheme 90



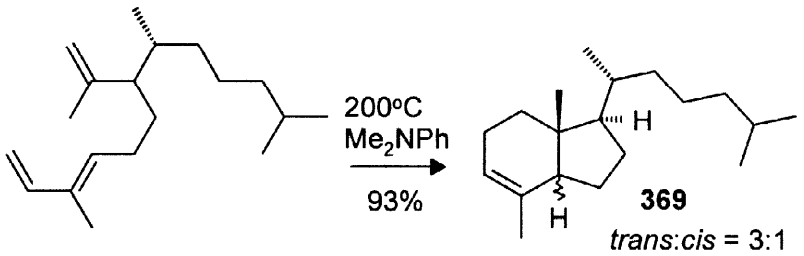
In the Parker and Iqbal[149] approach to the vitamin D hydrindane fragment, the key triene **367** was synthesized from divinyl alcohol **363** (Scheme 91). The required *ul* configuration on the chiral centres C_{17} and C_{20} was secured by the Horner–Wadsworth–Emmons reaction of aldehyde **364** with an anion generated from triethyl 2-phosphonopropionate, affording *E*-ester **365**, and then by the Ireland–Claisen rearrangement [250] of the appropriate derivative of **366**. The rearrangement yielded the corresponding trienoic acid, which was esterified, purified by chromatography (9% of the *lk* isomer was also isolated) and then subjected to the thermal Diels–Alder reaction. The

Scheme 91



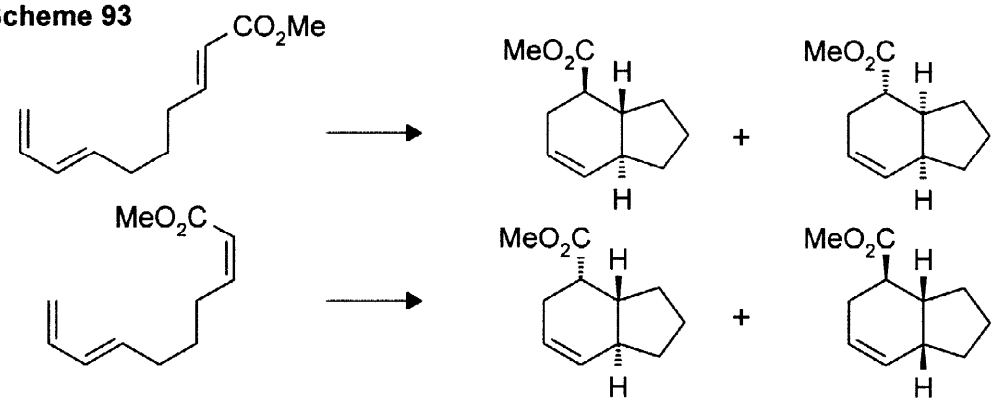
ester group in the immediate reaction product was reduced, and then the hydroxy group was esterified with 3,5-dinitrobenzoil chloride to give **368**. An equal mixture of *trans*- and cis-isomers was isolated.

Scheme 92



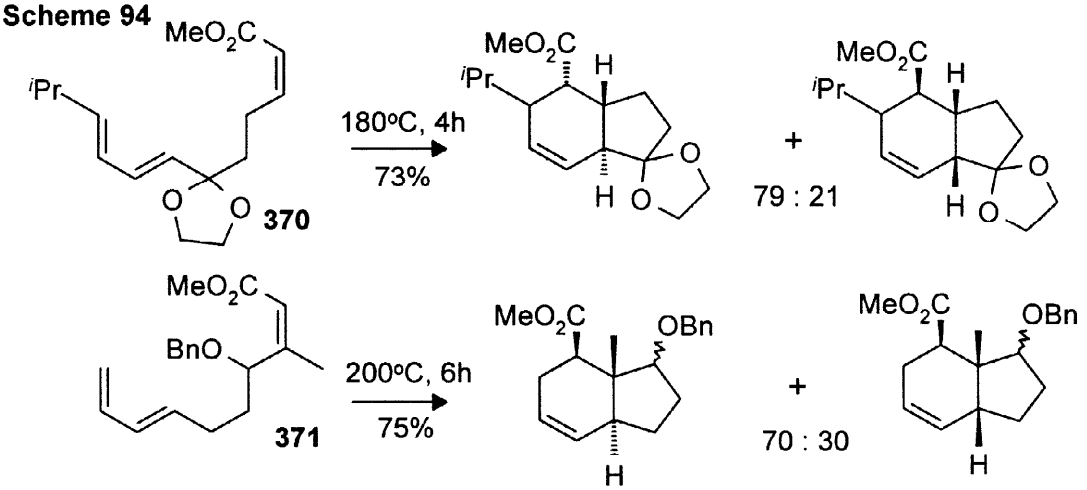
In the subsequent approach to the vitamin D synthesis by the same authors [251] dienes bearing a substituent at the latent position 8 were used (Scheme 92). The hydrindane derivative **369** was obtained from the corresponding triene in high yields and relatively high stereoselectivity (the results are shown in Scheme 92).

Scheme 93



Stereochemical aspects of the intramolecular Diels–Alder reactions of deca-2,7,9-trienoate esters leading to hydrindane derivatives were studied by Roush and co-workers.[252] It was found that thermal cyclization afford mixtures of adducts with the *trans*-fused products slightly dominating. Some examples are given in Scheme 93.

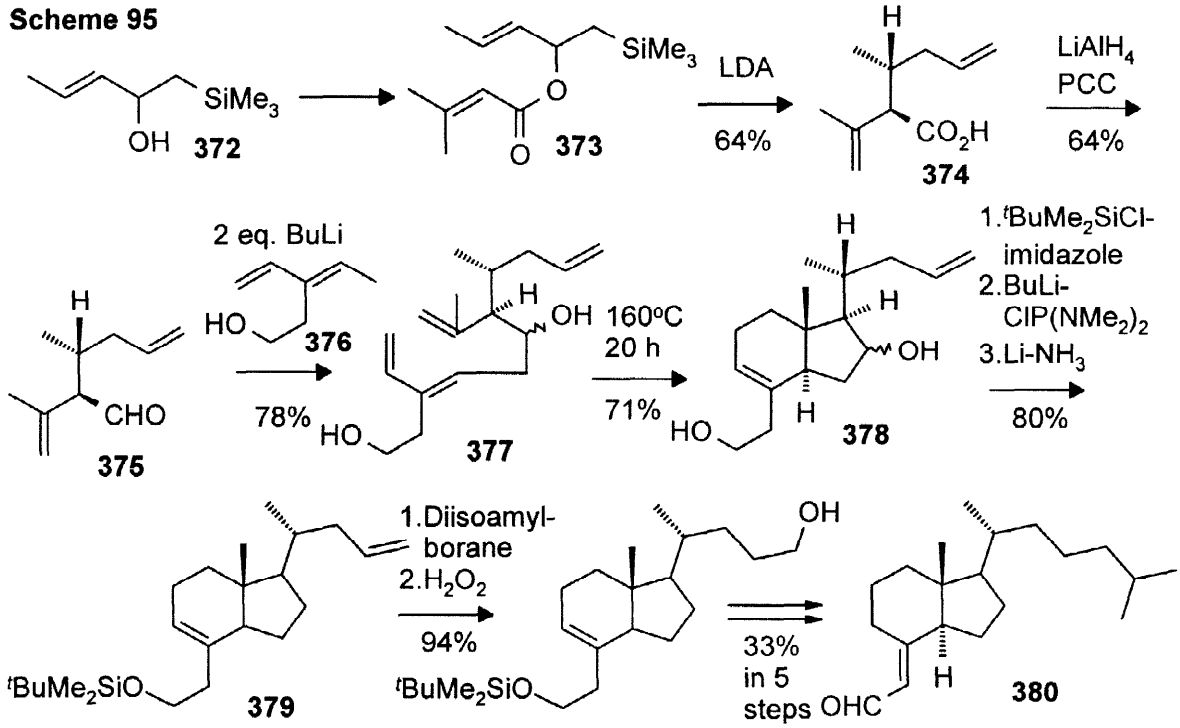
Scheme 94



Reactions of the ketal triene **370**[253] and those of the benzyloxy triene **371**[254] are of particular interest. Cyclization catalysed by various Lewis acids (particularly $AlClEt_2$) were more efficient (Scheme 94). It has been

shown that thermal intermolecular reaction inactivated 1,3,8-nonatriene occured with low stereo- selectivity and afforded mainly *cis*-products,[255] in contrast to the reactions discussed above. However, the trienes activated simultaneously by diethylamino group (the diene) and the carboalkoxy group (the dienophile) afforded the respective products with a clear predominance of the *trans*-isomers.[255,256]

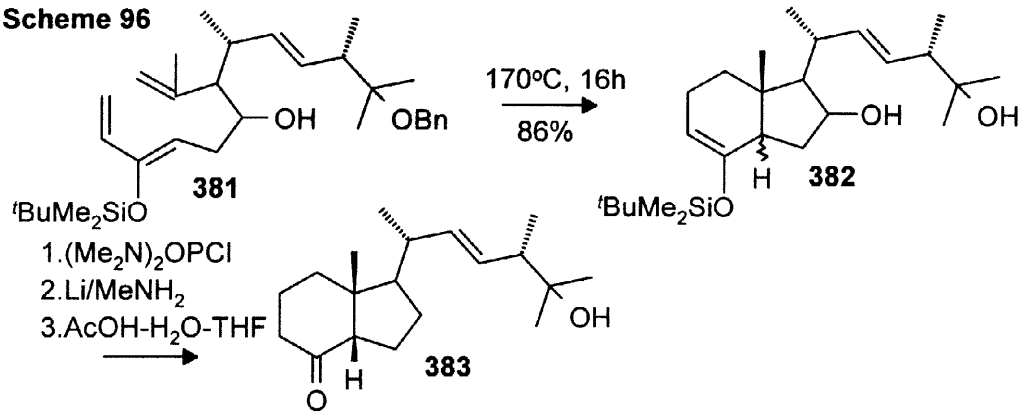
Scheme 95



In the synthesis of vitamin D hydrindane portion by Wilson *at al.*[257](Scheme 95), allylic alcohol bearing the trimethylsilyl group **372** (prepared from croton aldehyde and Me_3SiCH_2MgBr) was converted into ester **373**, which was then subjected to homo-Claisen rearrangement. The product **374** consisted of diastereomers in a ratio of at least 8:1 in favour of the required one with *lk* configuration at C_{17} and C_{20}. The aldehyde **375** was reacted with dianion generated from dienyl alcohol **376** to give **377** (with the epimers ratio 3:1). In the key step of the synthesis **377** underwent cycloaddition to yield the hydrindane derivatives. After chromatography, *trans*-**378** and the corresponding *cis*-isomer were obtained in 71% and 18% yields, respectively. In the further transformations, the primary hydroxy group in **378** was selectively protected whereupon the secondary hydroxy group was removed by the method of Ireland.[258] Thus obtained intermediate **379** was straightforwardly converted into aldehyde **380**. The authors have indicated that the enantioselective version of their synthesis could be based upon the Sharpless kinetic resolution of the starting allylic alcohol (**372**).

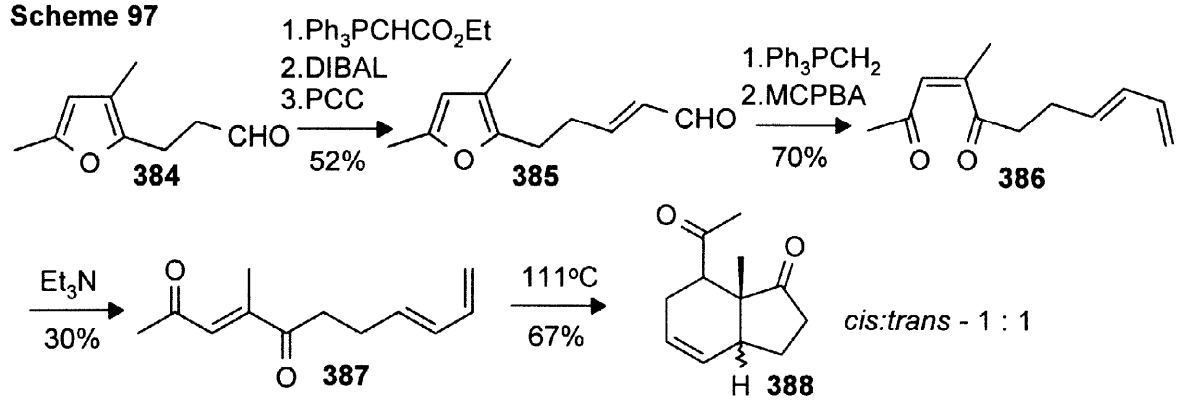
In the subsequent vitamin D synthesis from Willson's laboratory,[259] optically active tetraenic intermediate **381** was prepared in a similar way (Scheme 96). The heating of **381** in toluene afforded the cycloaddition product **382**, which, without isolation, was subjected to the hydroxy group removing procedure (which resulted also in deprotection of the C_{25} hydroxy group). The resulting product was treated with acetic acid in order to hydrolyse silyl enol ether moiety. Bicyclic ketone was obtained. However, it turned out that the product was the *cis*-hydrindanone **383**. It is probable that the cycloaddition of **381** afforded the corresponding *trans*-hydrindane and that the epimerization accompanied the hydrolysis of *tert*-butyldimethylsilyl group in the last stage of the synthesis. The *cis*-hydrindane **383** could be, in principle, transformed into its *trans* counterpart by one of the methods discussed above (cf. Schemes 18 and 25 and the relevant text).

Scheme 96



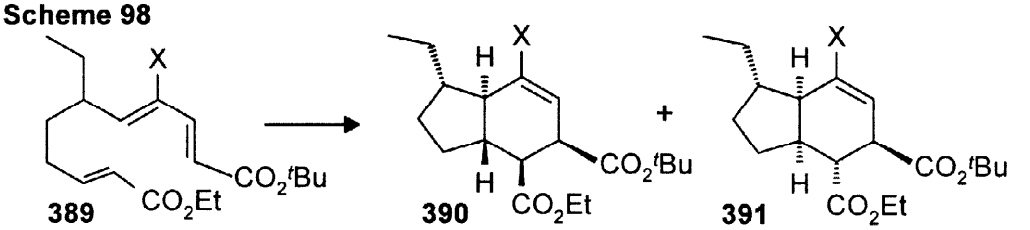
In the Williams and LeGoff[260] hydrindane synthesis, aldehyde **385** (Scheme 97) (prepared by acid-catalysed addition of acrolein to 2,5-dimethylfuran **384**) was transformed into triene **387**, using furan oxidation and endione isomerization of **386** as the key steps. Cyclization of **387** afforded the isomeric diketones **388**.

Scheme 97



Boeckman and Barta[261] have shown (Scheme 98) that the trimethylsilyl group may serve as a removable stereocontrol element in [4+2] cycloaddition leading to hydrindane derivatives. Cyclization of triene **389a**, X=H afforded a mixture of *cis*- and *trans*-products, **390a** and **391a**, in a ratio of 1:4, whereas the related triene with the trimethylsilyl group (**389b**) afforded exclusively the *trans*-product. The silyl group was efficiently removed from the products by the usual methods.

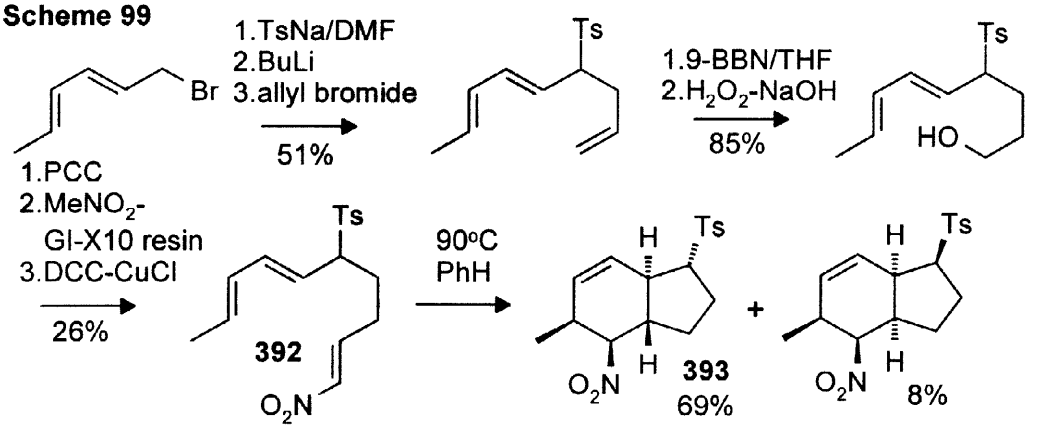
Scheme 98



a, X=H, **390** : **391** = 4:1
b, X=$SiMe_3$, exclusively **390** (85% yield)

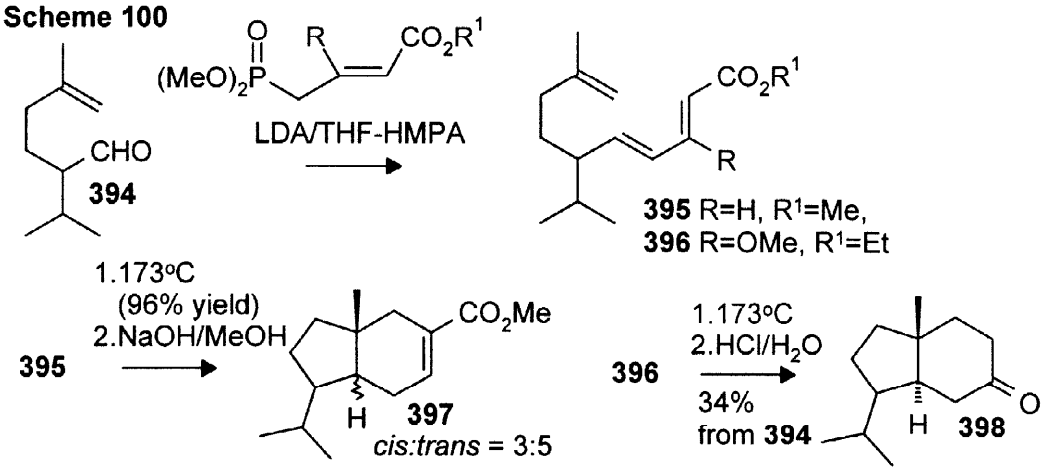
Relatively high diastereoselection in favour of *trans*-hydrindene **393** was achieved in the intramolecular cycloaddition reaction of the nitro-triene **392** (Scheme 99).[262] The synthesis of **392** involves the reaction of aldehyde with nitromethane in the presence of polymer-supported quaternary ammonium hydroxide catalyst (AGI-X10 resin) and then dehydration of the nitroaldol with DCC-CuCl.[263]

Scheme 99



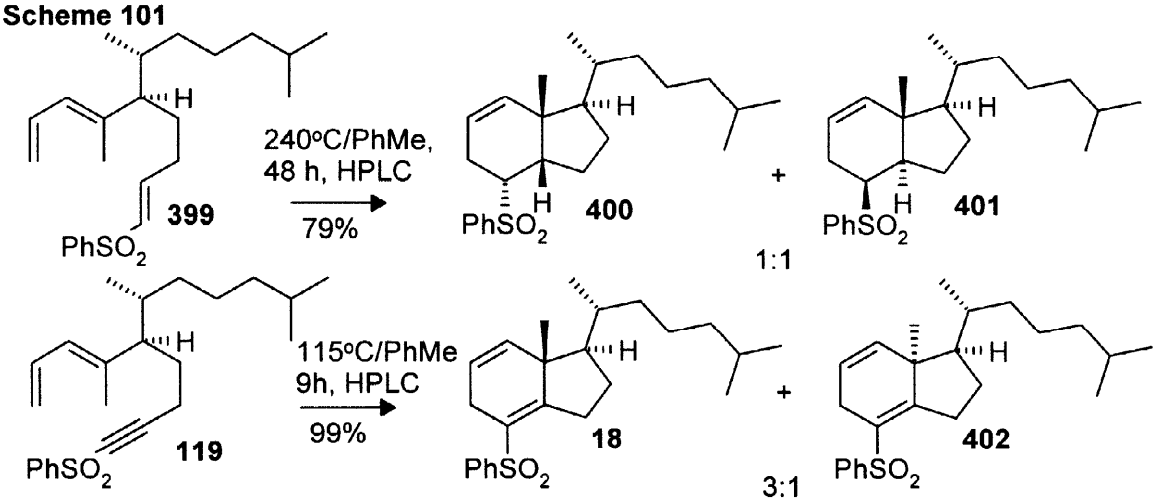
The substitution pattern of the diene portion may exert an important effect on the steric course of the cyclization. Thus, triene **395** yielded (after the double bond isomerization) a mixture of *cis*- and *trans*-products **397** (Scheme 100), whereas methoxy diene **396** gave only the *trans*-product **398** (after hydrolysis and decarboxylation).[218] It is noteworthy that the intermediate **394** was transformed into **398** using a sequence of reactions that involve the Michael reaction (see, Scheme 77 and the relevant text).

Scheme 100



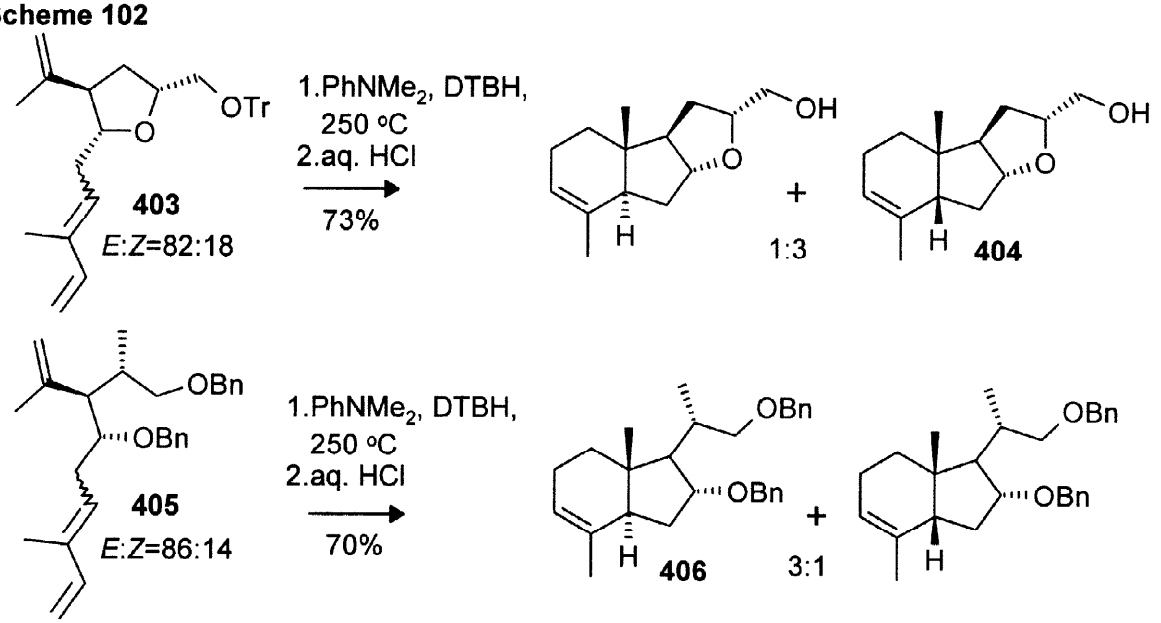
Craig *et al.*[24] have investigated the intramolecular Diels–Alder reactions of systems with an inactivated diene portion and ene or yne activated by the phenyl sulfonyl group, **399** and **119** (Scheme 101, for the synthesis of **399**

Scheme 101



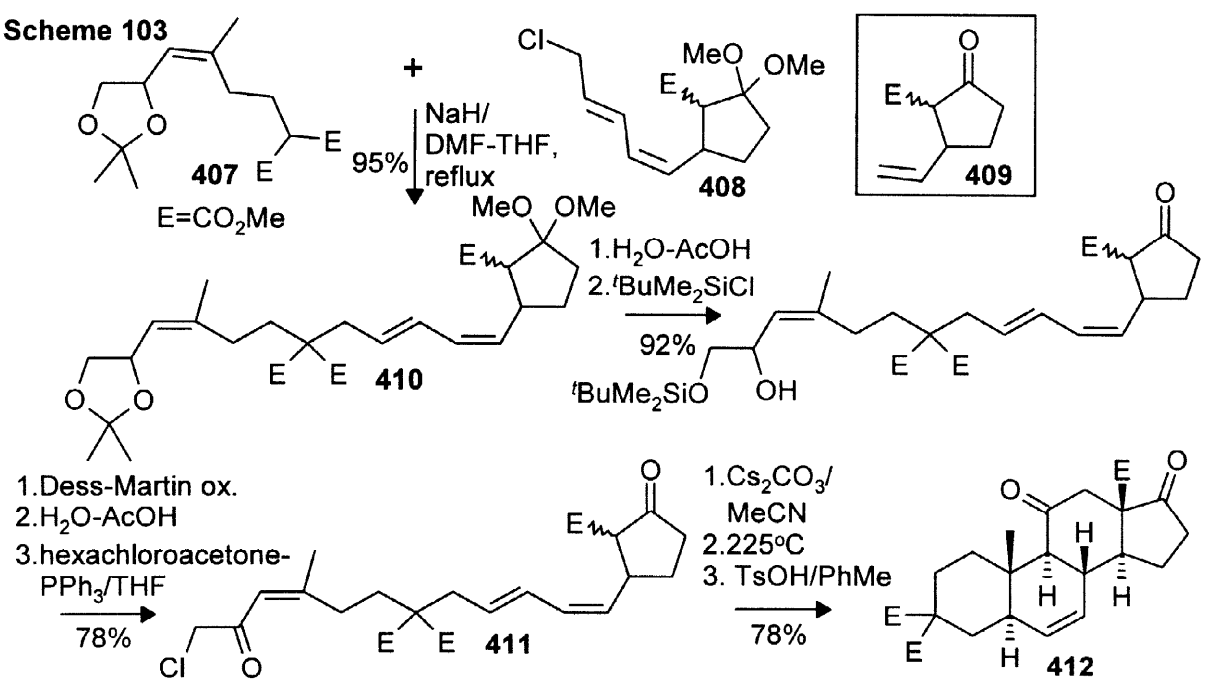
and **119**, see Scheme 26). The (*E*)-vinyl sulfonyl compound **399** showed low reactivity, however, at high temperature it afforded a 1:1 mixture of *cis*- and *trans*- fused bicyclic products **400** and **401** (which were separated by HPLC). The isomeric (*Z*)-vinyl sulfone underwent decomposition when heated in toluene at 180 °C. The diene-yne **119** underwent cyclization smoothly at 115 °C to give a mixture of *syn*- and *anti*- products **18** and **402** (3:1). Compound **18** was then efficiently transformed into C/D *trans*-saturated sulphone (**26**, Scheme 16, see also Schemes 25 and 28).

Scheme 102



An interesting example of substituent effect on the steric course of 1,3,8-nonatriene cyclization has been reported recently by Taber and Song.[264] While triene with a tetrahydrofuran unit **403** (Scheme 102) underwent thermal [4+2] cycloaddition to yield predominantly *cis*-fused hydrindane **404** (cis:*trans* ratio of 3:1), its acyclic

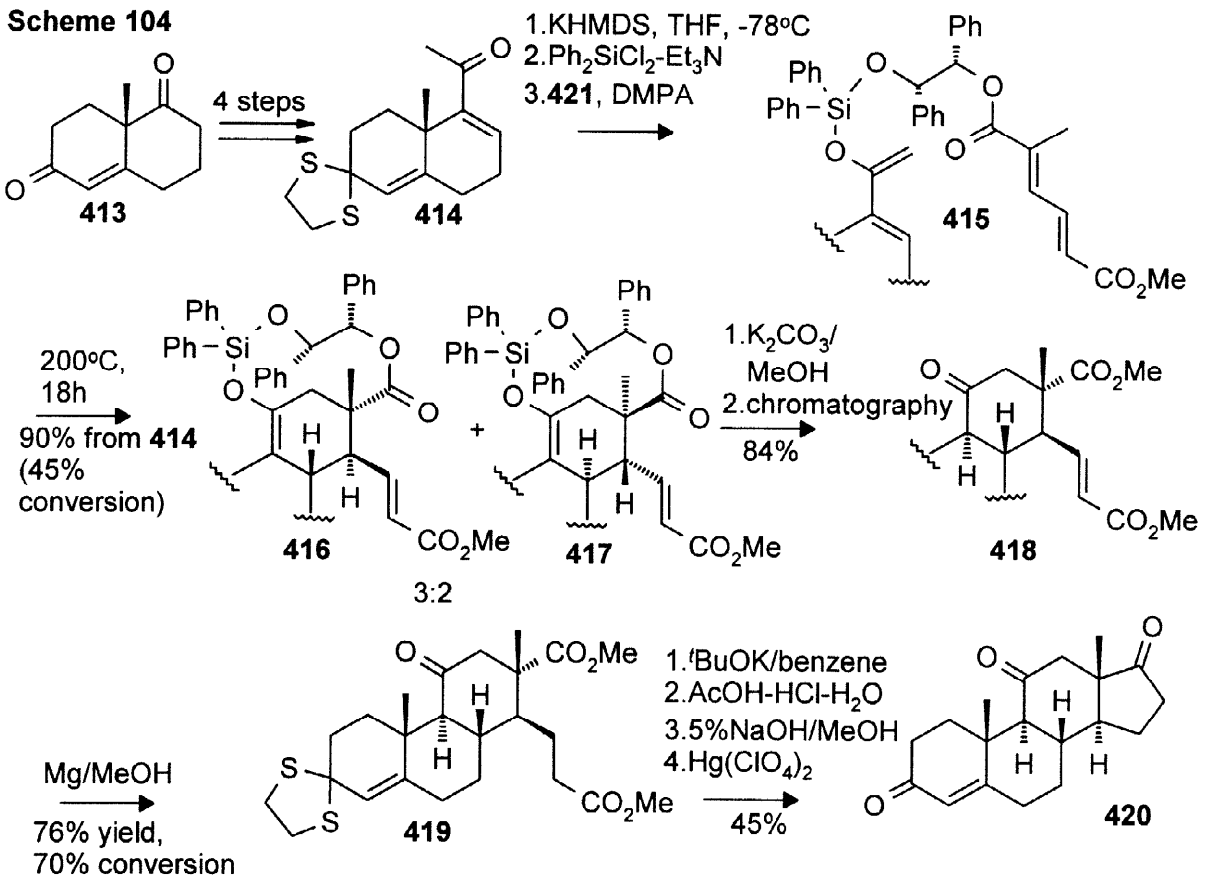
Scheme 103



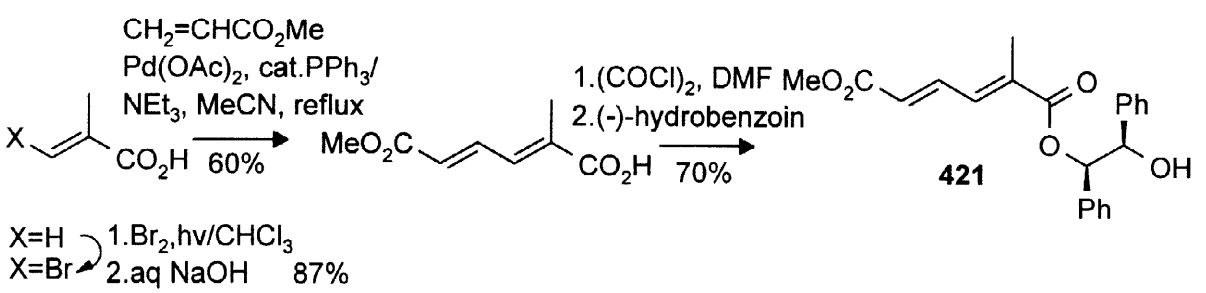
analogue **405** under similar conditions provided mainly the *trans* product **406** (*cis*:*trans* ratio of 1:3). This observation emphasizes the delicacy of the balance between the various factors that affect the stereochemistry of the Diels–Alder reaction of inactivated trienes.

Couturier and Deslongchamps[271,272] have reported a short approach to steroid **412** (Scheme 103). The diene **408**, prepared stereoselectively from 2-carbomethoxy-3-vinylcyclopentan-1-one (**409**) in five steps, was coupled with unsaturated malonate derivative **407** to yield triene **410**. Compound **410** was transformed into chloride **411**, which was subjected to macrocyclization using cesium carbonate in acetonitrile. The macrocyclic diene-ene was heated to afford tetracyclic product of the transannular Diels–Alder reaction and was isomerized at C_9 to the final product **412**.

Scheme 104



Synthesis of the dienophile **421**



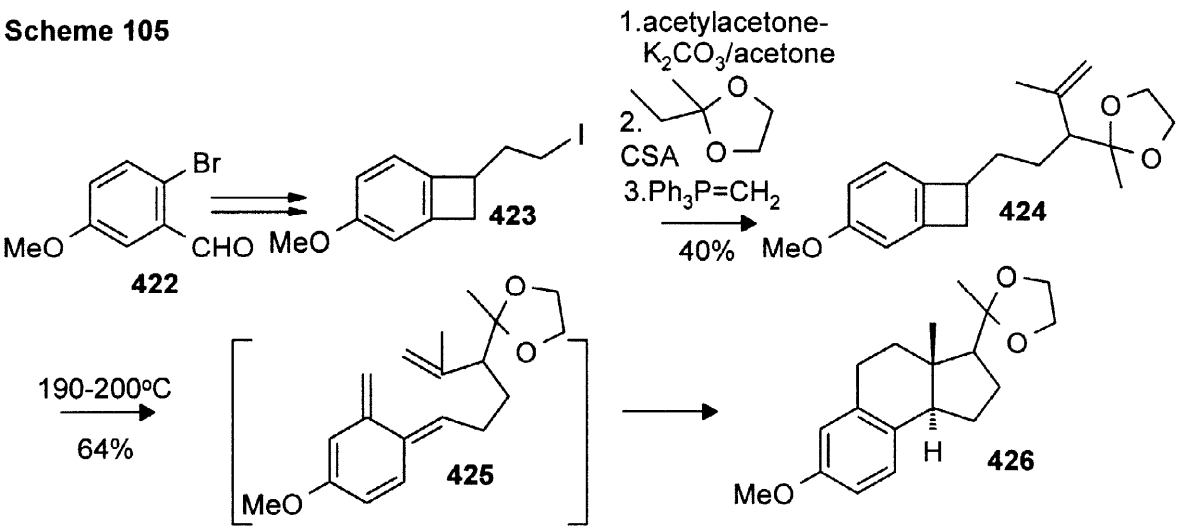
A short synthesis of (+)-adrenosterone **420** (Scheme 104), using the intramolecular Diels–Alder reaction with "a temporary connection", has recently been reported by Shea and coworkers.[273] Enone **414** (Scheme 104), prepared

from (+)-Wieland-Miescher ketone (**413**), was converted into its kinetic potassium dienolate and connected with the dienophile **421** using Ph_2SiCl_2 as the link. The intermediate thus constructed, **415**, is composed of the diene system; activated ene ; the easy to cleave silicon connection ; and the chiral auxiliary. The cycloaddition was carried out in toluene at 200 °C for 18 h to afford a 3:2 mixture of **416** and **417** in 90% yield (based on 45% conversion). Subsequent treatment of the adducts mixture with K_2CO_3/MeOH removed the silicon connection and chiral auxiliary to give the core of the tetracyclic product **418**. The unsaturated ester **418** was reduced with magnesium in MeOH. The diester **419** (obtained in 76% yield) was subjected to Dieckmann cyclization followed by decarboxylation to form ring D. After removal of the thioacetal protective group the final product **420** was obtained in 45% yield from **419**.

Cycloaddition of the *o*-quinodimethane unit and the isolated double bond has been widely applied to synthesis of polycyclic compounds[274-276] including hydrindane derivatives. An advantage of this method is the simultaneous formation of two rings. Since several reviews of the method are available [277] we have confined ourselves to a few examples, in which selective formation of *trans*-hydrindane rings was achieved (Schemes 105, 106, 107).

In an approach to des-A-steroid **426** (Scheme 105) Kametani *et al.*[278] used iodide **423**, obtained from 2-bromo-5-methoxybenzaldehyde (**422**). Acetylacetone was alkylated with iodide **423**, then one of the oxo groups was protected as an ethylene ketal and the other was reacted with methylenetriphenylphosphorane to give the key intermediate **424**. The heating of **424** at 190-200°C resulted in intramolecular cycloaddition *via* the *o*-quinodimethane derivative **425**. The product **426** with *trans*-configuration at the ring junction was obtained exclusively. The stereochemistry of the reaction was controlled by the substituent at the latent C_{17} carbon atom.

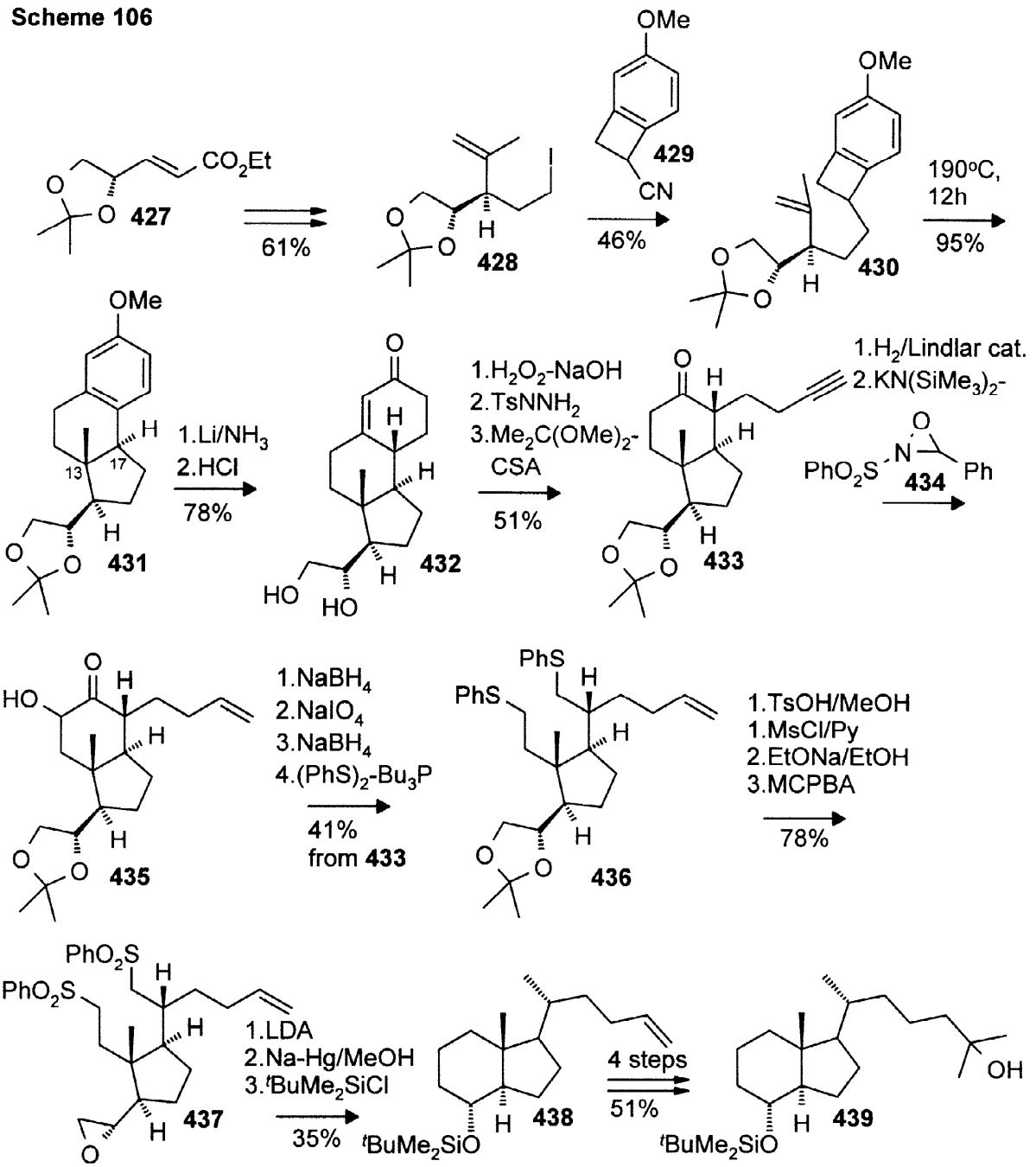
Scheme 105



A similar method was used to control stereochemistry at four consecutive asymmetric centres in the vitamin D precursor **439** [279] (Scheme 106). Conjugate addition of the isopropenyl group to optically active unsaturated ester **427** (prepared from D-mannitol) afforded diastereoselectively intermediate **428** (the required configuration at C_8 in the product was secured). Straightforward transformation of ester **428** into the corresponding primary iodide, followed by the coupling of the iodide with 1-cyano-4-methoxydihydrobenzocyclobutene **429** and reductive removal of the cyano group afforded **430**. The *o*-quinodimethane derivative generated on heating underwent the intramolecular cycloaddition to yield **431**. In this reaction two new chiral centres corresponding to positions 13 and 17 in the target compound were created. Further elaboration of the aromatic ring in **431** involved the Birch reduction

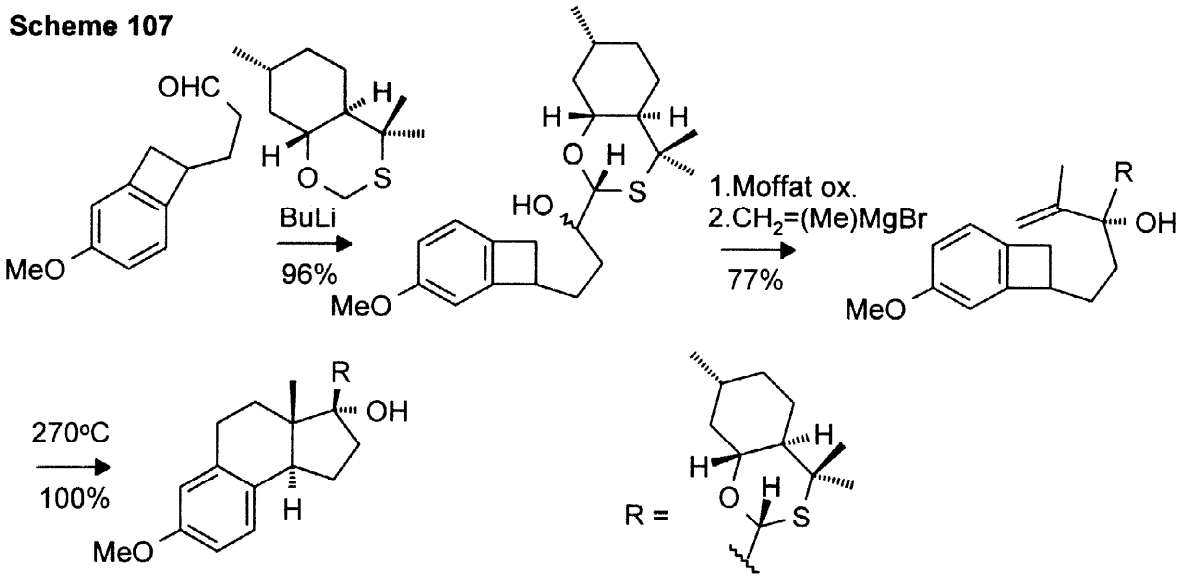
to give **432**. Enone **432** was epoxidized and the intermediate epoxy ketone was subjected to the Eschenmoser cleavage. The triple bond in **433** was partly hydrogenated and then the resulting product was hydroxylated in α-position to the carbonyl group using N-phenylsulphonyloxaziridine **434**[280] (the configuration was not indicated) to afford the intermediate **435**, which was transformed into monocyclic compound **436**. The closure of ring C was achieved by regioselective intramolecular reaction of epoxy disulphone **437** to give compound **438**. The whole synthesis involved 25 steps and afforded the final product in about. 1% yield.

Scheme 106



Another recent example of the use of *o*-quinomethane approach for the construction of *trans*-hydrindane ring is shown in the Scheme 107[281]. To achieve enantioselectivity Eliel's chiral auxiliary[282] was used.

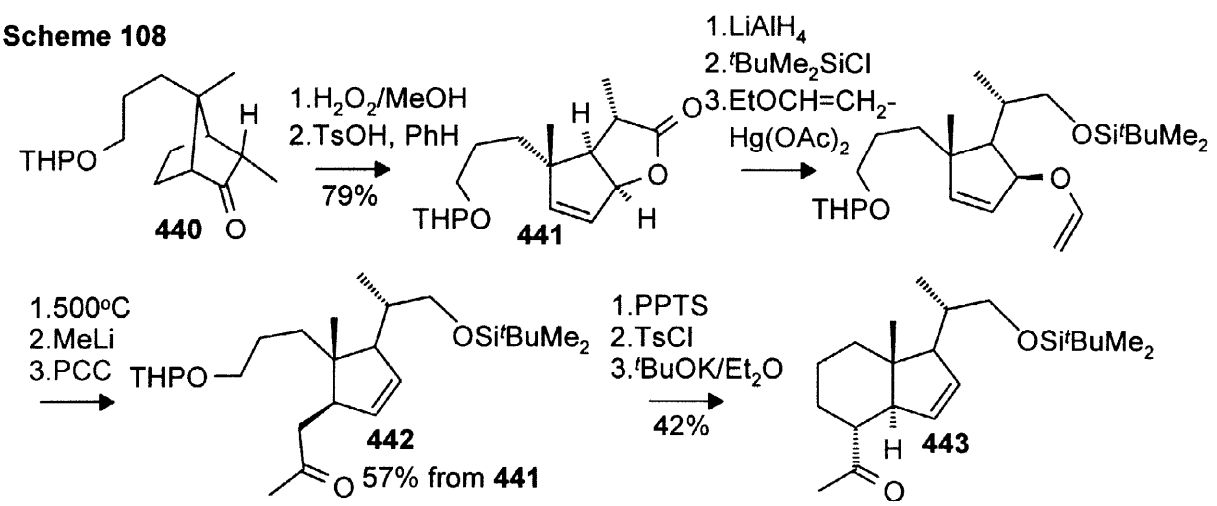
Scheme 107



7.2. Claisen and Cope and related rearrangements[283,284]

Intramolecular cyclization of the cyclopentane derivative **442** (Scheme 108) to afford *trans*-hydrindane derivative **443** was reported by Trost and coworkers.[285] The intermediate **442** was prepared from bicycloheptane **440** as indicated in the Scheme 108.

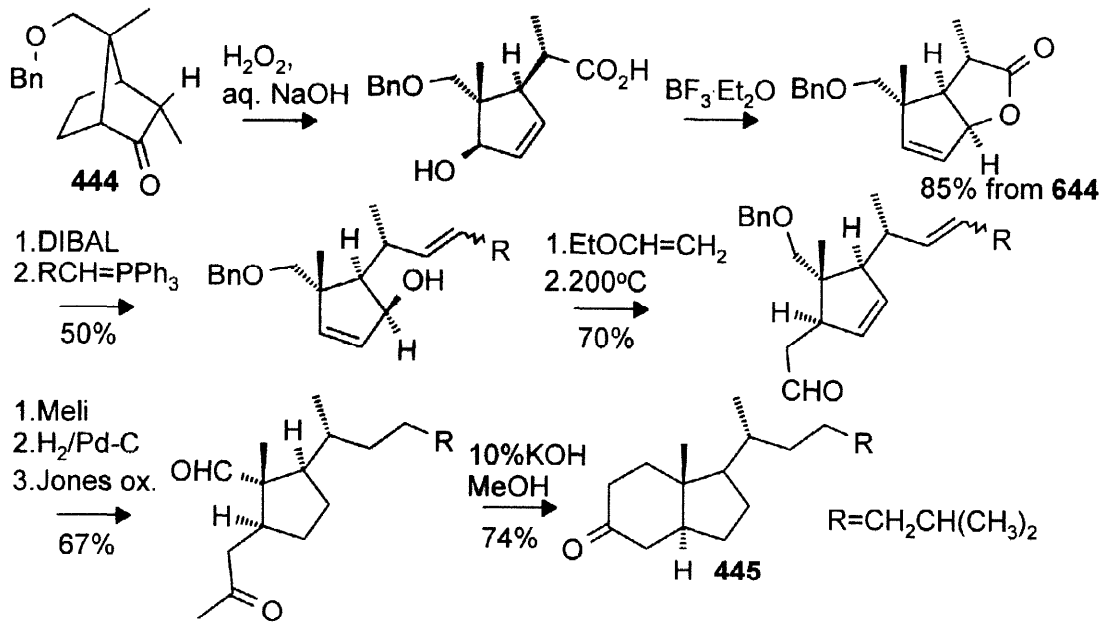
Scheme 108



A similar principle was applied in a short synthesis of des-AB-cholestane-9-one **445** developed by the Grieco group (Scheme 109).[286,287]

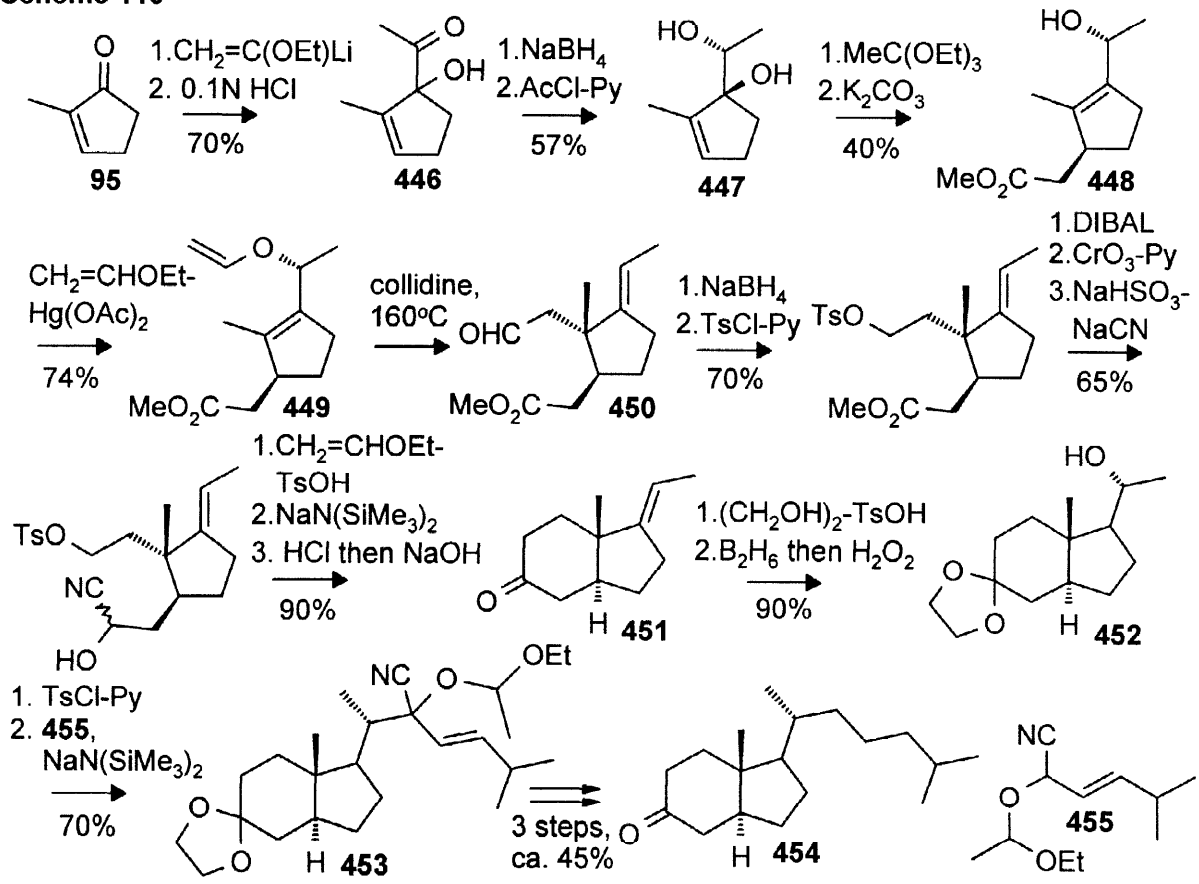
A stereoselective approach to AB-des-9-oxocholestane involving diastereoselective reduction of the carbonyl group and two consecutive Claisen rearrangemets occurring with 1,3-chirality transfer was reported by Takahashi *et al.*[288,289] Reduction of hydroxy ketone **446** (Scheme 110) with $NaBH_4$ afforded the *uk* diastereomer of **447** (80%) accompanied by a small amount of the *lk* diastereomer (8%). After chromatographic purification of the main product and protection of the secondary hydroxyl group in the form of acetate, the Claisen rearrangement was performed.

Scheme 109



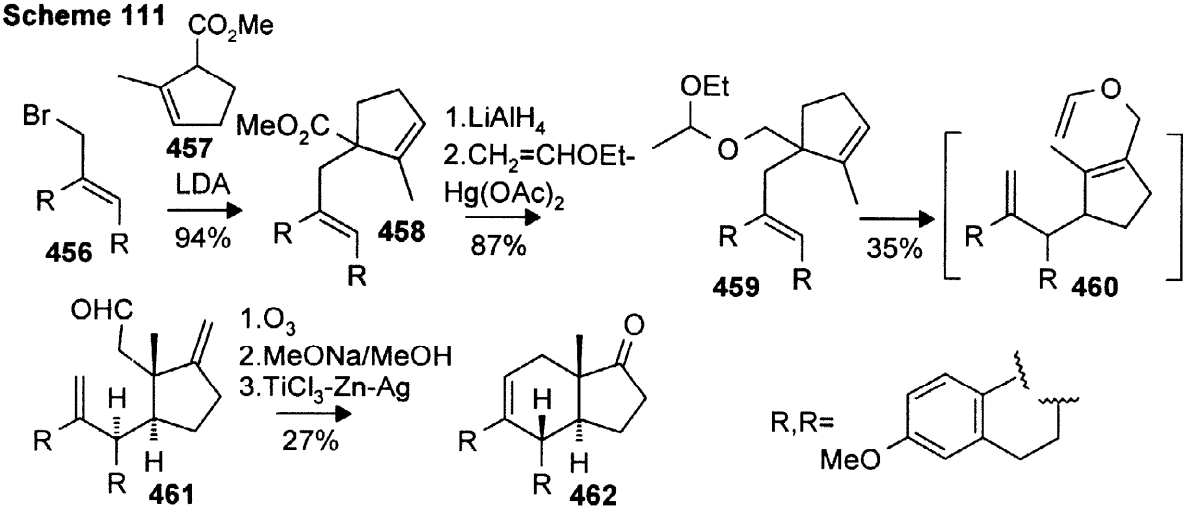
Methanolysis of the acetate function afforded **448**. Generation of vinyl ether (**449**) and subsequent Claisen rearrangement furnished the intermediate **450** with the required configuration of substituents around the cyclopentane ring. The ring was then closed using the Stork cyanohydrin method.[290] Hydroboration of the double

Scheme 110



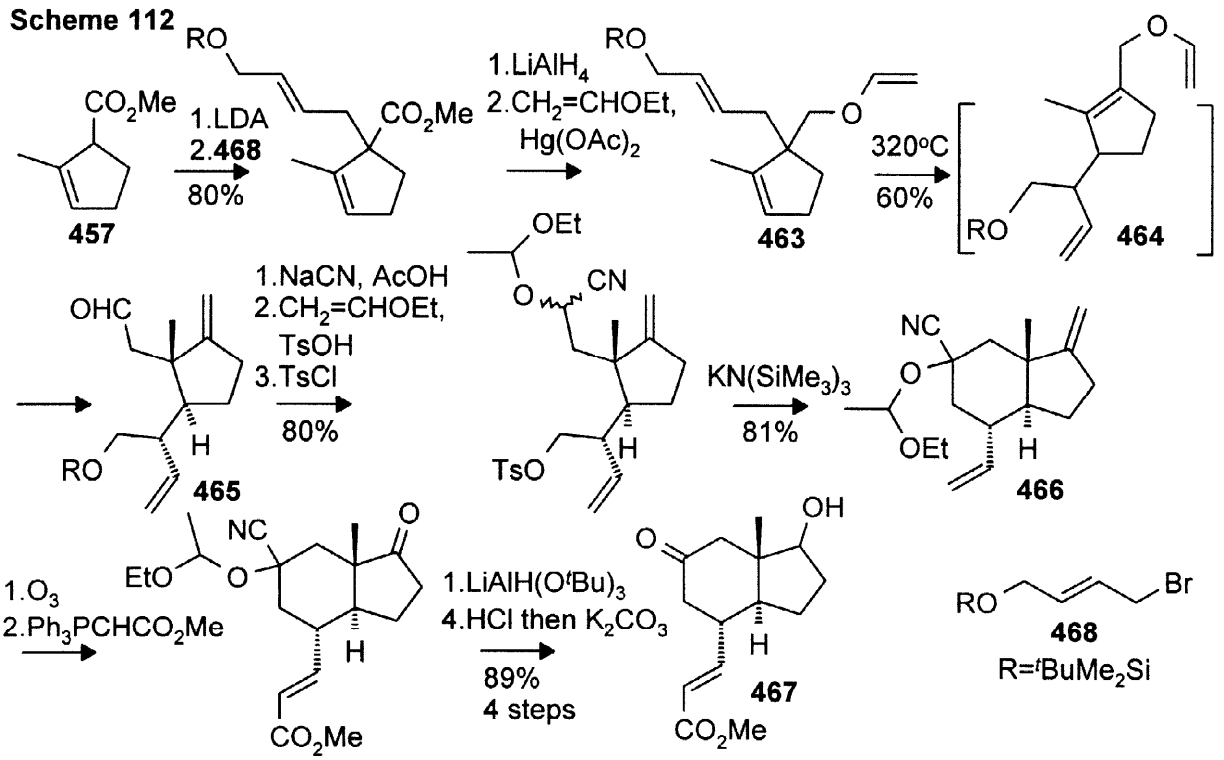
bond in **451** occurred virtually stereoselectively to give alcohol **452**, which was tosylated[291] and coupled with the C_{22}-C_{27} fragment **455**. The intermediate **453** was transformed into AB-des-cholestane derivative **454** using known procedures.[292]

Scheme 111



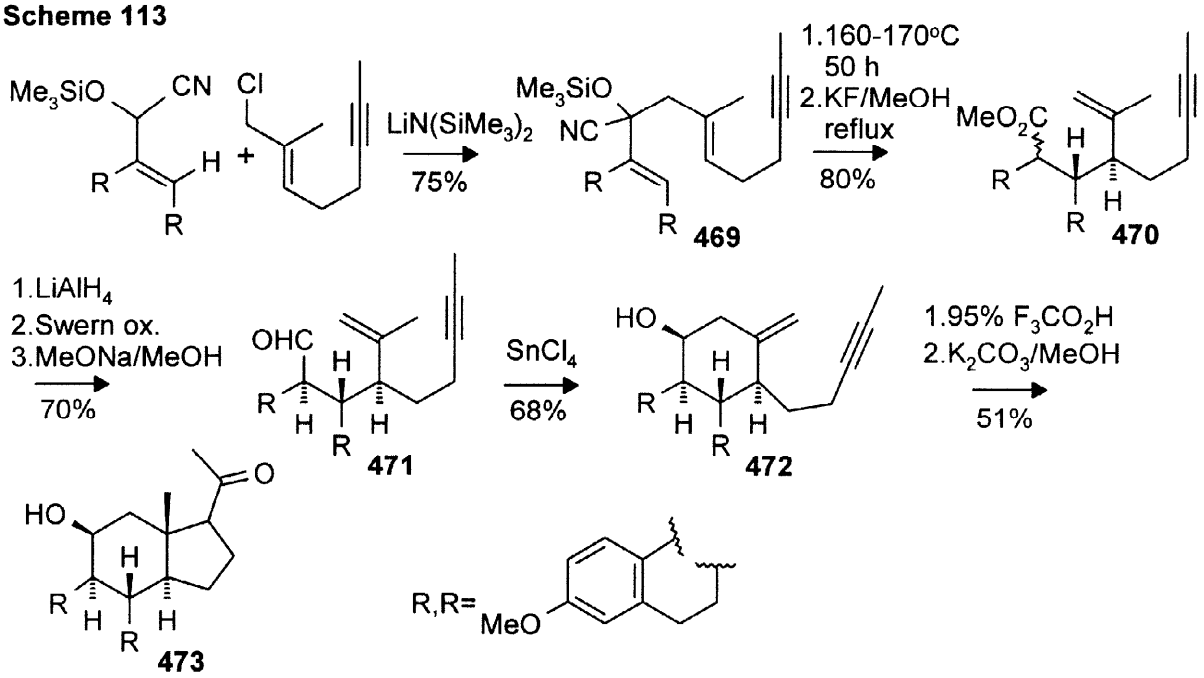
Alkylation of allylic bromide **456** (Scheme 111) with an anion generated from 2-methyl-2-cyclopentene-1-carboxylate **457** gave 1,5-diene **458**.[293] The ester group in **458** was reduced and the resulting alcohol was transformed into acetal **459**. The heating of **459** resulted in the Cope rearrangement, leading to the vinylic ether intermediate **460**, which on Claisen rearrangement to afforded compound **461** with *syn-trans* configuration of the chiral centres. Ozonolysis of **461** provided the tricarbonyl intermediate, which was treated with a base in order to epimerise the chiral centre at C_8. Finally, the ring C was closed using McMurry procedure to give the estrone derivative **462**.

Scheme 112



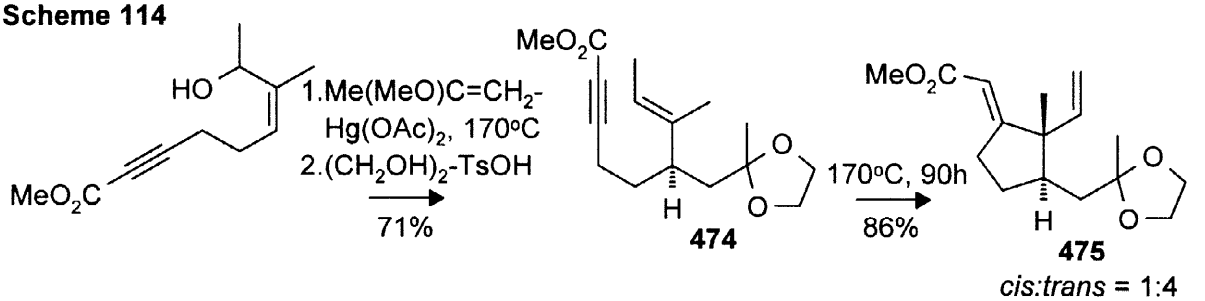
1,5-Diene **463** (Scheme 112) was envisioned as a *trans*-hydrindane precursor.[294,295] On heating it underwent the Cope rearrangement to afford the intermediate **464**, which in turn rearranged into **465**. The product **465** was obtained in 60% yield along with its *cis*-isomer (14%, not shown). Further transformations of **465** into steroid building block **467** involved ozonolysis of diene **466** and the selective Horner–Wadsworth–Emmons reaction at the aldehyde group.

Scheme 113



The Cope rearrangement of diene **469** (Scheme 113) followed by hydrolysis of the cyanohydrin moiety afforded the intermediate **470** with the correct relative configuration at the latent C_8 and C_{14} positions.[296,297] Construction of ring C and then ring D was based upon acid catalysed ene reaction. Thus, the treatment of **471** with tin tetrachloride effected cyclization yielding **472**. Compound **472** was cyclised with trifluoroacetic acid to give the *trans*-hydrindane derivative **473**.

Scheme 114

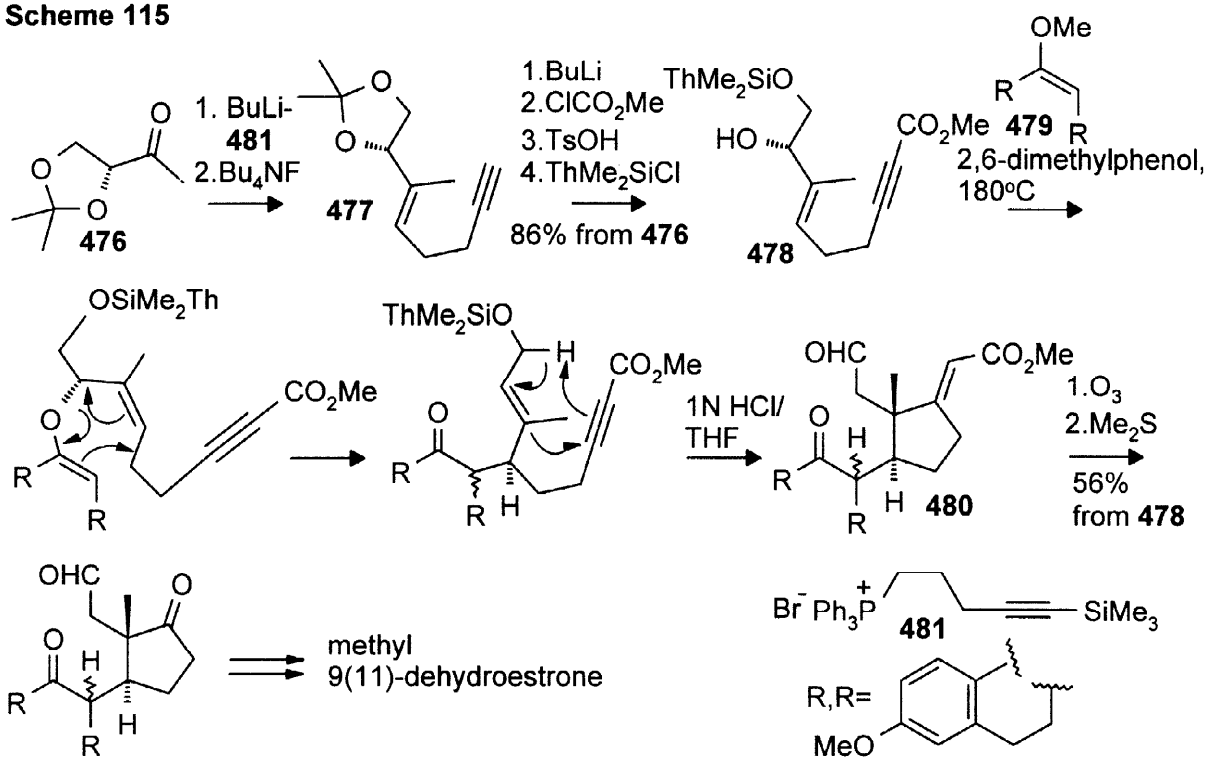


Mikami and coworkers[298] have shown that the Claisen rearrangement and the ene reaction may be used in tandem to synthesise the *trans*-hydrindane precursor **475** (Scheme 114). Thermal rearrangement and cyclization of **474** gave **475** accompanied by its cis isomer (*cis-trans*:1:4).

Ketone **476**, prepared from (*R*)-glyceraldehyde, was reacted with an ylid generated from **481** to give selectively the olefin **477** (Scheme 115).[299] After methoxycarbonylation and protective group manipulation, the thextyldimethylsilyl derivative **478** was treated with **479** in toluene containing 10 mol% of 2,6-dimethylphenol at

180 °C. The product of the tandem Claisen-ene reaction **480** was obtained in 76% yield (after hydrolysis of the protective group). Configuration of the product was confirmed by its transformation into estrone derivative (cf. Scheme 67 and Scheme 111).

Scheme 115

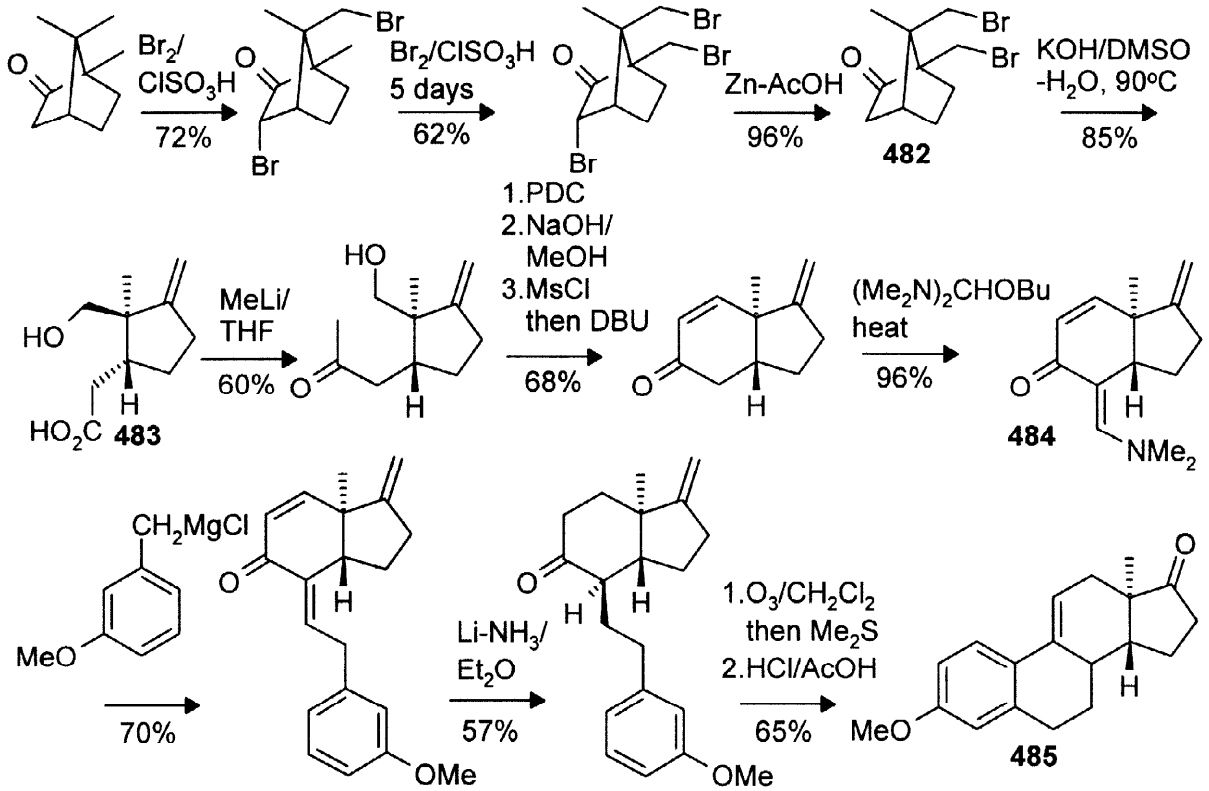


7.3. Comments on hydrindane synthesis from optically active [2.2.1]-bicycloheptane derivatives

The syntheses of steroid and vitamin D compounds from bicycloheptane derivatives, involving chirality transfer, have already been discussed in other sections (Schemes 20, 108 and 109). Several important steroids have been approached by Money and coworkers using (+)-camphor as the optically active starting material, essentially preserving the original chiral centres.[300] The use of this readily available starting material revolves around the alkali-induced ring cleavage of dibromocamphor (Scheme 116, **482**) to generate cyclopentane building block **483**. The symmetry elements of this compound with the methyl group at the quaternary carbon atom made possible the construction of a steroid hydrindane unit of natural *ent*-configuration. The synthesis of *ent*-estrone derivative **485** (Scheme 116) may serve as an an example of work of this group. On one or two points some comments are in order. Regioselective addition of *m*-methoxybenzyl group to the cross conjugated enone **484** should be noted. It has been reported that an attempt to use the corresponding methylene derivative (H in place of NMe_2) failed.

In some other approaches to steroids by the Canadian group, the $-CH_2CO_2H$ moiety of **483** was used as the side chain precursor. The chiral centre corresponding to C_{14} had to be then created at the carbon atom bearing the methylene group.

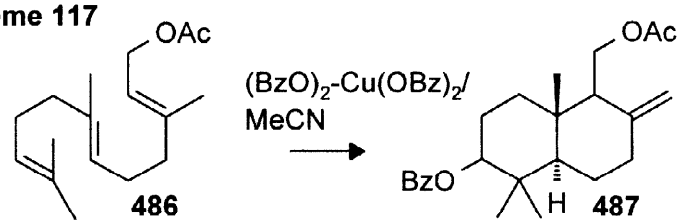
Scheme 116



8. Free-radical cyclization

Breslow and coworkers[301] reported in 1968 that *trans,trans*-farnesyl acetate **486** (Scheme 117) treated with benzoil peroxide in acetonitrile under free-radical reaction conditions,[302] with cupric benzoate added to provide a termination mechanism, undergoes bicyclization to the decalin derivative **487**. The thermal or photochemical variants afforded the same product in 30% or 5% yield, respectively.

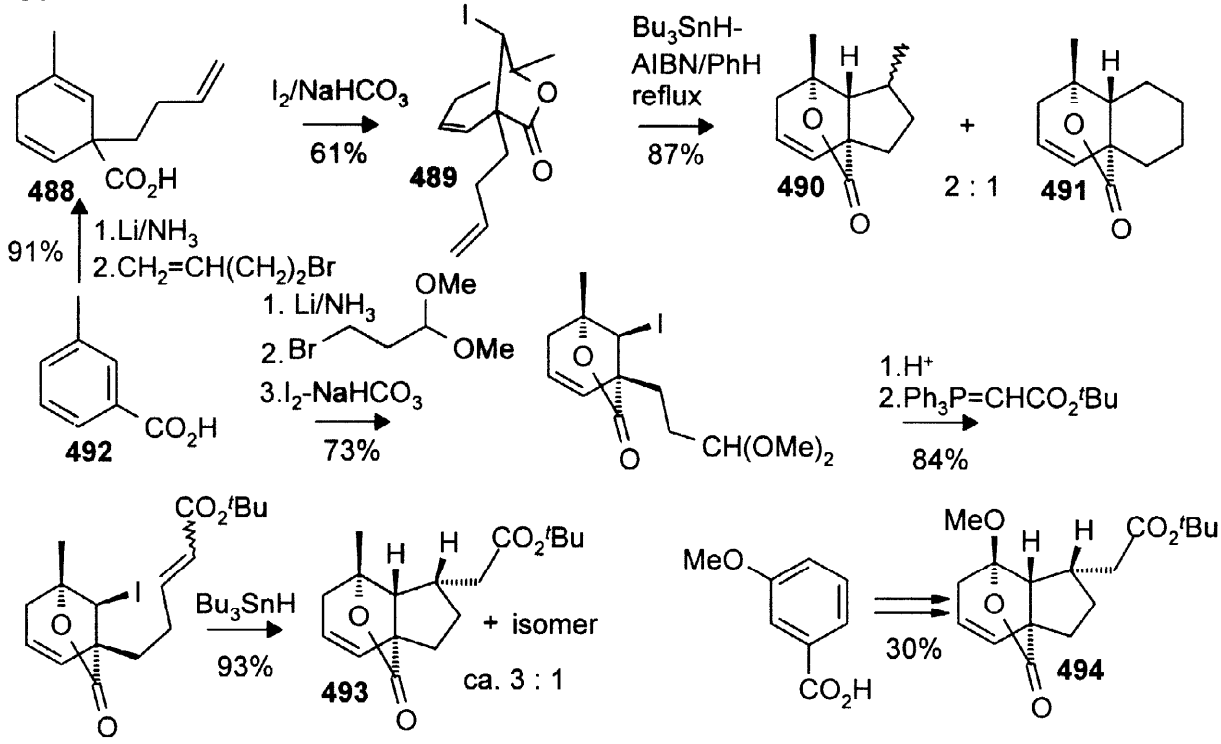
Scheme 117



thermal reaction 20 - 30% yield
photochemical 5% yield

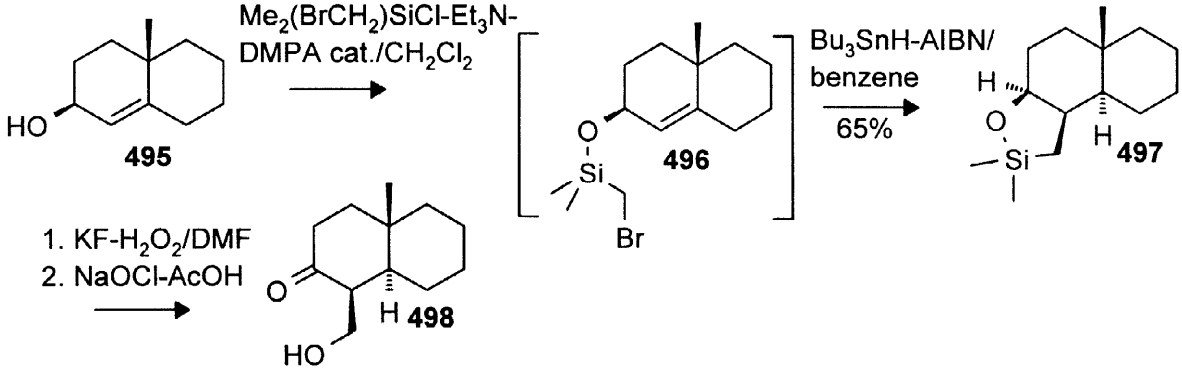
A synthetic approach to *trans*-hydrindane derivatives based on radical cyclization has been developed by Chuang and Hart[303]. The Birch reduction of *m*-toluic acid, **492** (Scheme 118), followed by alkylation of the resulting dianion with 1-bromobut-3-ene afforded **488**. This compound was subjected to iodolactonization to give **489** with a 1-iodohex-5-ene system. Reductive cyclization of **489** resulted in a mixture of hydrindane and decalin derivatives, **490** and **491** in a ratio of 2:1. Formation of a relatively large proportion of the 6-*endo*-product **491** is noteworthy, given the preference for 5-*exo*-cyclization with acyclic 1-halohex-5-enes. More complex hydrindane derivatives **493** and **494** were synthesized as shown in Scheme 118 to demonstrate the versatility of the method.

Scheme 118



Stork and coworkers have developed a method for controlling the decalin and hydrindane ring junction stereochemistry in free radical cyclizations by applying "temporary connections". Thus, allylic alcohol **495** (Scheme 119) was converted[304,305] into a silyl ether **496**, which was reduced with Bu_3SnH to give tricyclic acetal **497** in 65% overall yield. Oxidative cleavage of the C-Si bond[306,307] in **497**, followed by oxidation of the secondary hydroxy group afforded **498**. It should be noted that the transition-state geometry for radical cyclization can only lead to the *cis* fusion of the new five-membered ring (**497**). However, the overall process accomplished *trans*- addition to the allylic alcohol double bond with the hydrogen atom introduced from the least sterically congested face, *anti* to the original hydroxy function.

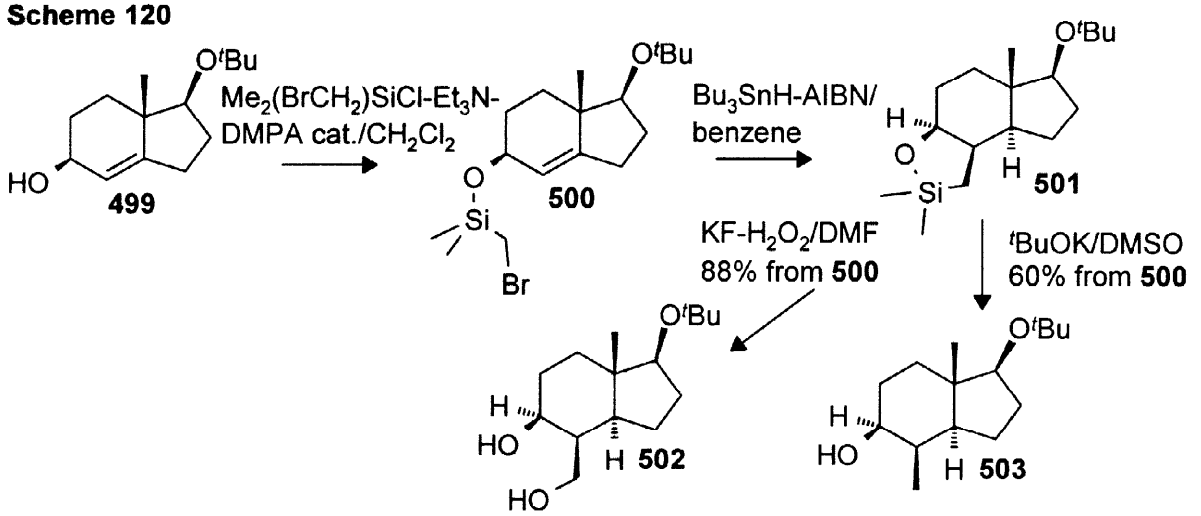
Scheme 119



In a similar way the hydrindane derivative **499** (Scheme 120) was transformed[308] into an intermediate with temporary silicon connection **500** and then by reduction with Bu_3SnH its[309] into the tricyclic intermediate **501**.

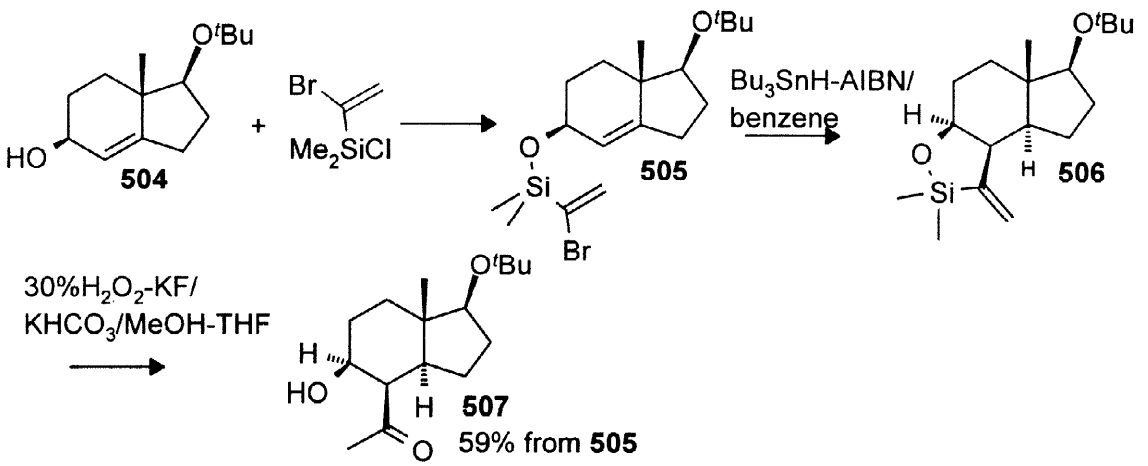
Compound **501** was subjected to desilylation or to oxidative desilylation to give the methyl or hydroxymethyl derivative, **502** or **503**, respectively, in good yields.

Scheme 120



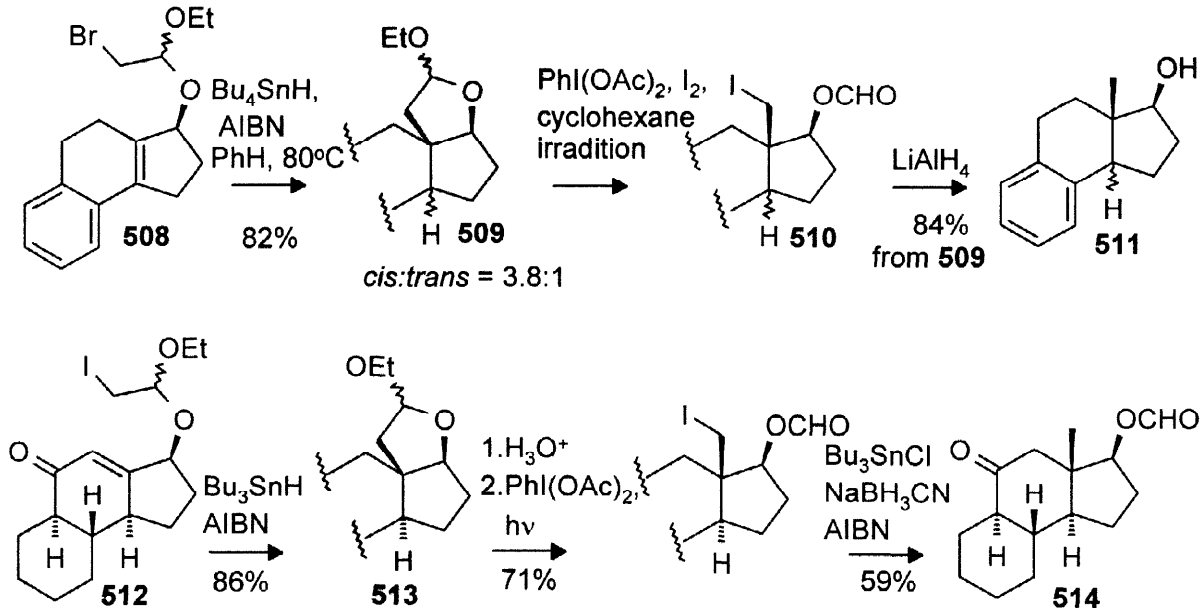
The same principle was applied to bromovinylsilane derivatives[310]. Thus, allylic alcohol **504** was reacted with (bromovinyl)chlorodimethylsilane to give the intermediate **505** which was subjected to free radical reaction. The product **506** was transformed into the vitamin D precursor **507** using the Fleming–Tamao oxidation[306](Scheme 121).

Scheme 121



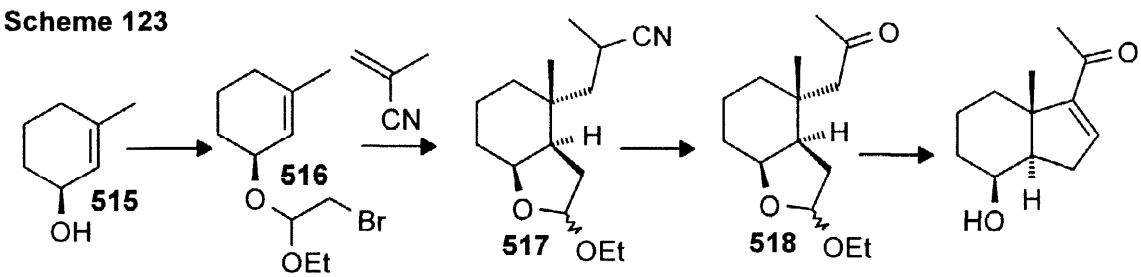
This technique was also used to introduce an angular methyl group into a hydrindane system. [311] Allylic bromoacetal **508** (Scheme 122) upon reduction with Bu_3SnH underwent reductive cyclization to give a mixture of *cis*- and trans-products with the former predominating. An interesting method was devised for transforming of the acetal **509** into its derivative with the angular methyl group (**511**). It involved C-C bond cleavage on irradiation of **509** in the presence of iodobenzene diacetate and iodine, and then $LiAlH_4$ reduction of the iodo formate **510** . In a similar way iodoacetal **512** under conditions of radical cyclization afforded the product **513** (with *trans*-fused hydrindane rings), which was then efficiently transformed into the derivative with the angular methyl group **514**.

Scheme 122



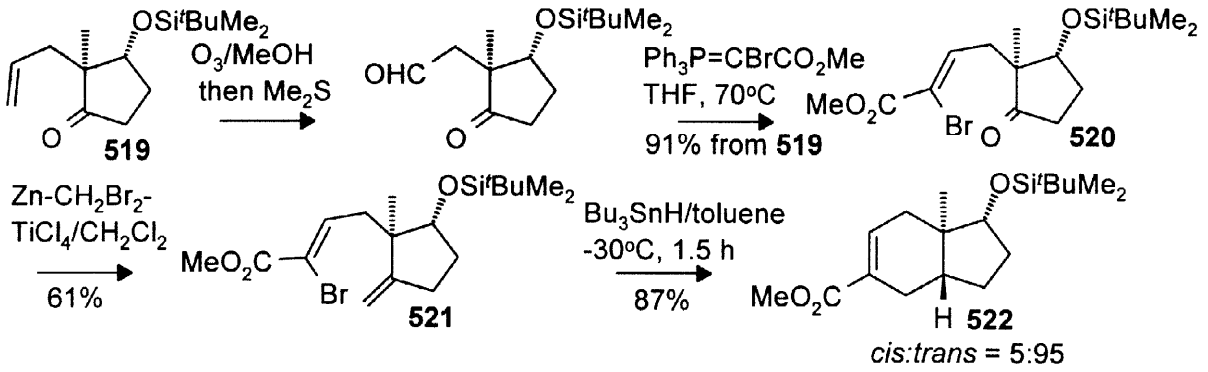
Stork *et al.*[223] have reported the synthesis of the vitamin D hydrindane fragment from optically active 3-methylcyclohex-2-en-1-ol **515** (Scheme 123). The key step in this synthesis (**516** →**517**) consisted of free radical addition of bromoacetaldehyde unit attached to the ene moiety by a temporary connection. The quaternary free radical formed in this process is trapped by propenyl nitrile. Transformation of nitrile **517** into ketone **518** and ring closure by aldol condensation completed the synthesis. The optically active starting material **515** was prepared using various enantioselective approaches. No experimental details were given.

Scheme 123



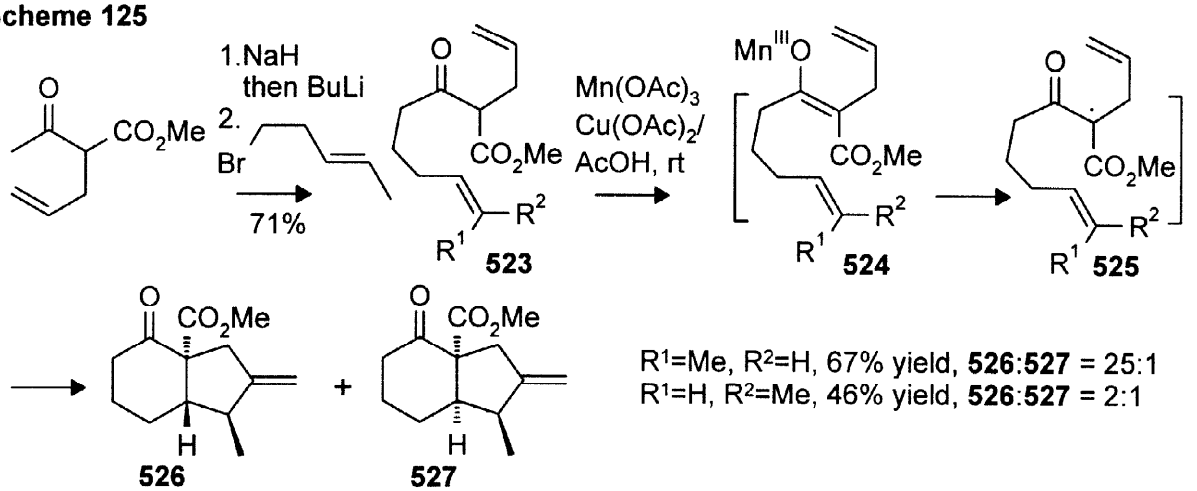
A method for free radical closure of a six-membered ring leading to *trans*-hydrindane derivatives has been reported Satoh *et al.*[312] Easily accessible [313] optically active vinyl cyclopentanone **519** (Scheme 124) was transformed into bromo ester **520** (*E*:*Z*=1:7) and then the oxo group was replaced with CH_2 using the Zn-CH_2Br_2-$TiCl_4$ reagent.[314] Bromo-1,5-diene **521** on treatment with Bu_3SnH underwent cyclization to afford **522** (the 6-*endo* product) in excellent yield and stereoselection. The product was contaminated with traces of the dihydro- and the 5-*exo*-products. It was of crucial importance for this cyclization that the tin hydride was added slowly to the reaction mixture. It is well documented that 1,5-hexadienyl radical cyclization afford kinetically controlled 5-*exo* products. However, the authors made use of the observations[315] that cyclization mode is changed when the hydride concentration is maintained low. It was suggested that the kinetically preferred 5-*exo* radical undergoes rearrangment to the thermodynamically more stable 6-*endo* one.

Scheme 124



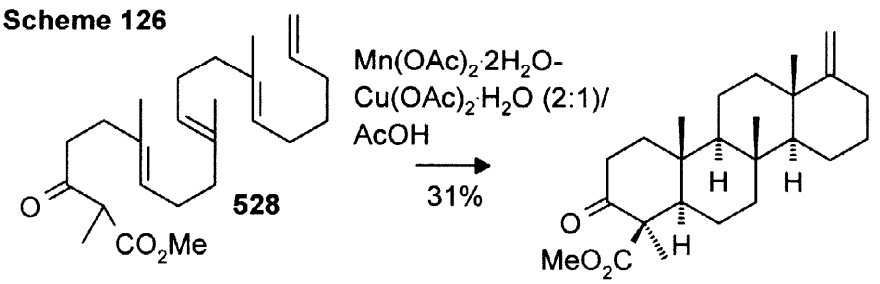
A promising new method of the synthesis of various bicyclic compounds consists of Mn^{III}-induced free-radical cyclization.[316,317] Selected examples of such reactions are given in Scheme 125. It is noteworthy that cyclization of the compound with (*Z*)-configuration of the double bond **523** occurred with high diastereoselection. Mechanistically, the reaction of **523** involved manganese enolate **524** and free radical **525** which cyclised by the 6-*endo* mode. The second cyclization (5-*exo*) was followed by oxidative elimination with $Cu(OAc)_2 \cdot H_2O$. This method offers an approach to highly functionalised *trans*-hydrindane derivatives.

Scheme 125



An example[318] of the generation of several asymmetric centres in one step using $Mn(OAc)_3$ - induced cyclization of keto ester **528** is shown in Scheme 126.[319]

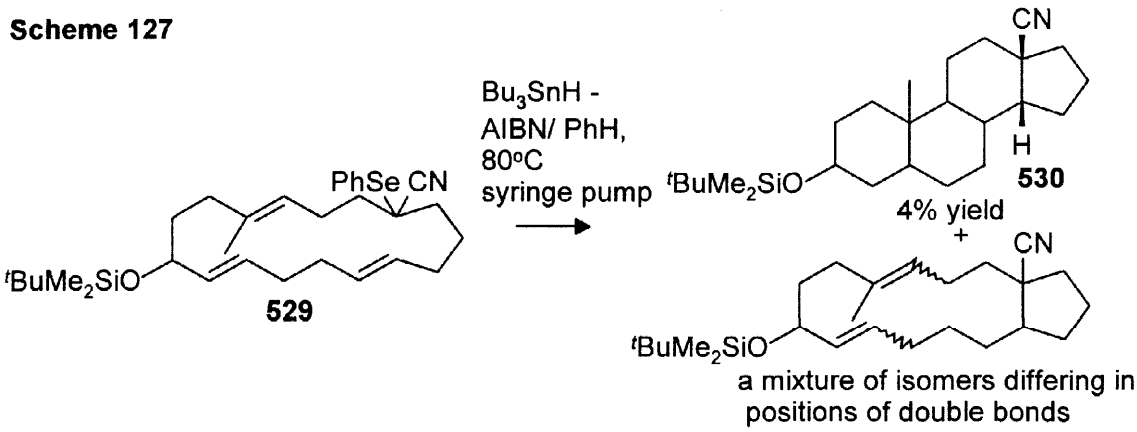
Scheme 126



A different approach to free radical based synthesis of polycyclic compounds was initiated by Jahn and Curran[320]. Macrocylic triene, equipped with a phenylselenyl moiety **529** (Scheme 127) was synthesized and then treated with tributyltin hydride (with slow addition of the reagent by a syringe pump). A complex mixture of

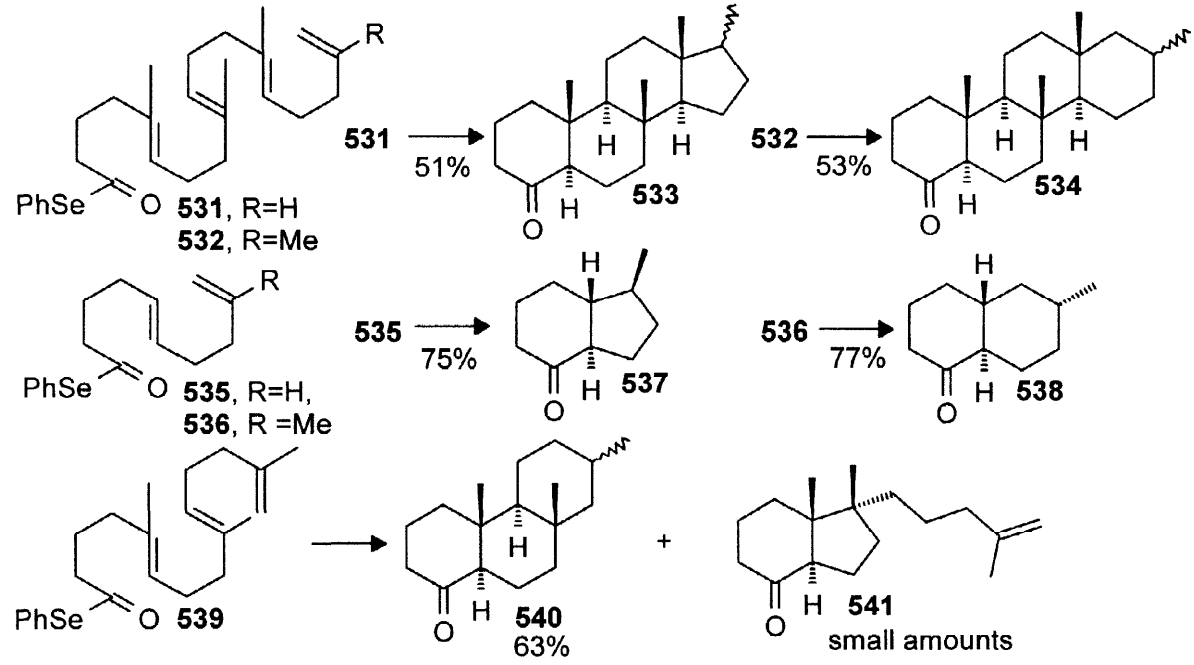
monocyclic compounds was formed as a result of transannular (1,5)-hydrogen transfer involving allylic positions. However, the tetracyclization product **530** could be isolated in 4% yield.

Scheme 127



Efficient free radical-initiated tetracyclization of tetraene **531**, leading to the 8-methyl-steroid derivative **533** (mixture of isomers at C_{17}, 51% yield, Scheme 128) with *trans*-hydrindane system, has recently been achieved by Pattenden and coworkers.[321] An analogous tetraene **532** with the methyl group on the terminal double bond, underwent cyclization to afford D-homo-8-methyl steroid **534**. The presence of the methyl group on the double bonds in the starting polyene was found to determine the regiochemical outcome of free radical cyclization. Thus, 1,5-diene **535** provided the corresponding hydrindane derivative **537** (75%) by 6-*endo*, 5-*exo-trig* cyclization whereas the methyl derivative **536** gave decalin **538** by two consecutive 6-*endo-trig* cyclizations. Similarly, **539** underwent 6-*endo-trig* tricyclization to give the tricyclic derivative **540** accompanied by only a small amount of the product of 6-*endo*, 5-*exo*-bicyclization (**541**).

Scheme 128



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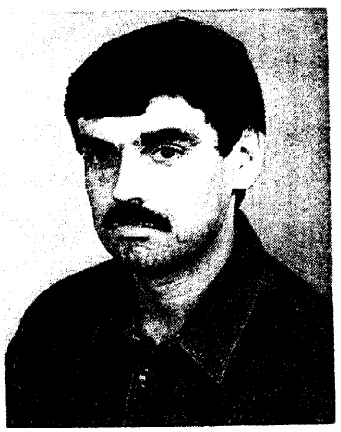

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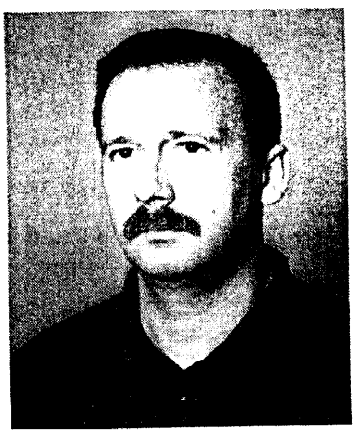

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