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Enantioselective synthesis of steroids

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Abbreviations: acac, acetylacetonate; 9-BBN, 9-bora-bicyclo[3.3.1]nonane; BHT, 2,6-di-*tert*-butyl-4-methylphenol; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; Binol, 1,1′-binaphthalene-2,2′-diol; Bn, benzyl; Boc, di-*tert*-butyl dicarbonate; CBS, (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo-[1,2-*c*]-[1,3,2]oxazaborole-borane; CDI, carbonyl diimidazole; CSA, camphor-10-sulfonic acid; Cp, cyclopentadienyl; dba, dibenzylideneacetone; DAST, (diethylaminosulfur) trifluoride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD, diethyl azodicarboxylate; DIBALH, diisobutylaluminum hydride; DMA, *N*,*N*-dimethylacetamide; DMAP, 4-dimethylaminopyridine; DMS, dimethylsulfide; DNB, 2,4-dinitrobenzoate; 2,4-DNPH, 2,4-dinitrophenylhydrazine; DPH, 3,4-dihydro-2*H*-pyran; dppb, 1,4-bis(diphenylphosphino)butane; dppf, 1,1′-bis(diphenylphosphino)ferrocene; ed, ethylenediamine; EDTA, ethylenediaminetetraacetic acid; ee, enantiomeric excess; EE, ethoxyethyl; HMPA, hexamethylphosphoramide; IPC_2BH, diisopinocampheylborane; KHMDS, potassium (bis(trimethylsilyl)amide); LAH, lithium aluminum hydride; LDA, lithium diisopropylamide; LiHMDS, lithium (bis(trimethylsilyl)amide); L-Selectride®, lithium tri-*sec*-butylborohydride; *m*-CPBA, 3-chloroperbenzoic acid; MEM, 2-methoxyethoxymethyl; MPM, 4-methoxybenzyl; MOM, methoxymethyl; Ms, methanesulfonyl; MS, molecular sieve; MW, microwave; NCS, *N*-chlorosuccinimide; Nf, nonafluoro-1-butanesulfonyl; NIS, *N*-iodosuccinimide; NMO, *N*-methylmorpholine oxide; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; PhMe, toluene; PMBOH, 4-methoxybenzyl alcohol; PPL, porcine pancreas lipase; PPTS, pyridinium *para*-toluenesulfonate; $Pr(hfc)_3$, praseodymium(III) tris[3-(heptafluoropropylhydroxymethylene)-d-camphorate]; PTSA, *para*-toluenesulfonic acid; Pv, pivaloyl; Red-Al®, sodium bis(2-methoxyethoxy)aluminum dihydride; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TES, triethylsilyl; TFA, trifluoroacetyl; Tf, trifluoromethanesulfonyl; 2-Th, 2-thienyl; THF, tetrahydrofuran; THP, tetrahydropyran-2-yl; Tm, 2,4,6-trimethylbenzenesulfonyl; TMED, tetramethylethylenediamine; TMS, trimethylsilyl; TPP, *meso*-tetraphenylporphyrin; Tr, triphenylmethyl; Triton® B, benzyltrimethylammonium hydroxide; Ts, *para*-toluenesulfonyl.

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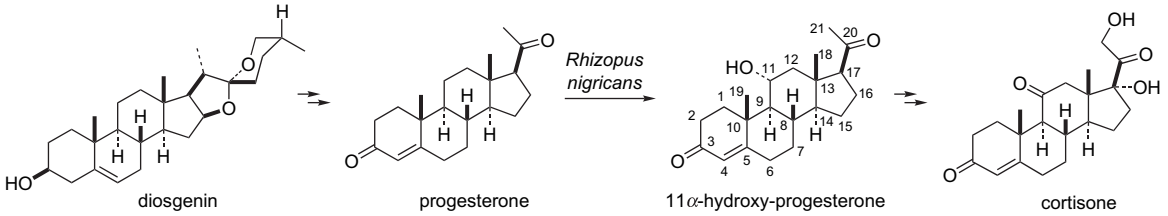
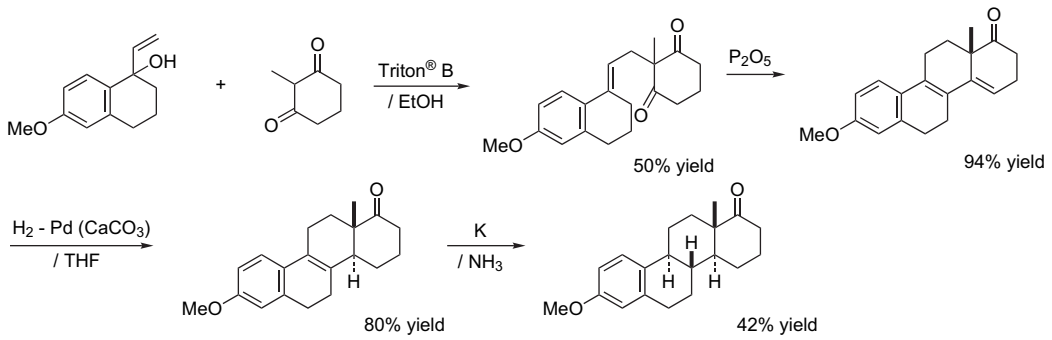
1. Introduction

The existence of steroids has been known for more than a century with the isolation of cholesterol from gall stones by Chevreul in 1815,[1] the elucidation of its chemical structure by Windaus in 1932,[2] and the first total synthesis of equilenin accomplished by Bachmann in 1939 taking advantage of Butenandt's ketone.[3] With their discovery probably dating from ancient times and their chemical characterization in the 1930s,[4] vitamins D have also largely contributed to the incontestable explosion of interest in steroid chemistry. Several research groups, including those of Elisabeth Dane and Robinson, have investigated various synthetic methods for the preparation of steroids, such as intermolecular Diels–Alder or aldol cyclization, and have proposed a variety of new structural motifs.[5] For a long time, however, only racemic approaches or modifications of natural sources were employed by chemists, considering that only a few efficient asymmetric methods were available to control the formation of stereogenic centers.[6] Thus, the hemisynthesis of progesterone reported in 1947 by Marker, from sapogenins extracted from agaves of Mexico and the Southern United States, has revealed as a major breakthrough in modified steroid synthesis.[7] In 1952, Peterson[8] showed that microbiological hydroxylation of progesterone by the mushroom, *Rhizopus nigricans*, occurred regio- and stereoselectively at the C(11) position[9,10] opening up a route to the preparation of cortisone,[11] the so-called 'wonder drug' (Scheme 1).[8]

Since 1959, the total synthesis of steroids has become applicable in industrial production mainly thanks to the discovery by Torgov of a process making possible the assembly of a steroidal A/B bicyclic core derived from 6-methoxy-1-tetralone with D-rings. The condensation was described for the first time with methylcyclohexanedione in the presence of Triton® B as a base to give a seco-C tricyclic intermediate that cyclized to form the Torgov diene and was converted into D-homoestrone (Scheme 2).[12] This cyclization step promoted by dehydrating agents or acidic catalysts was



Scheme 1.



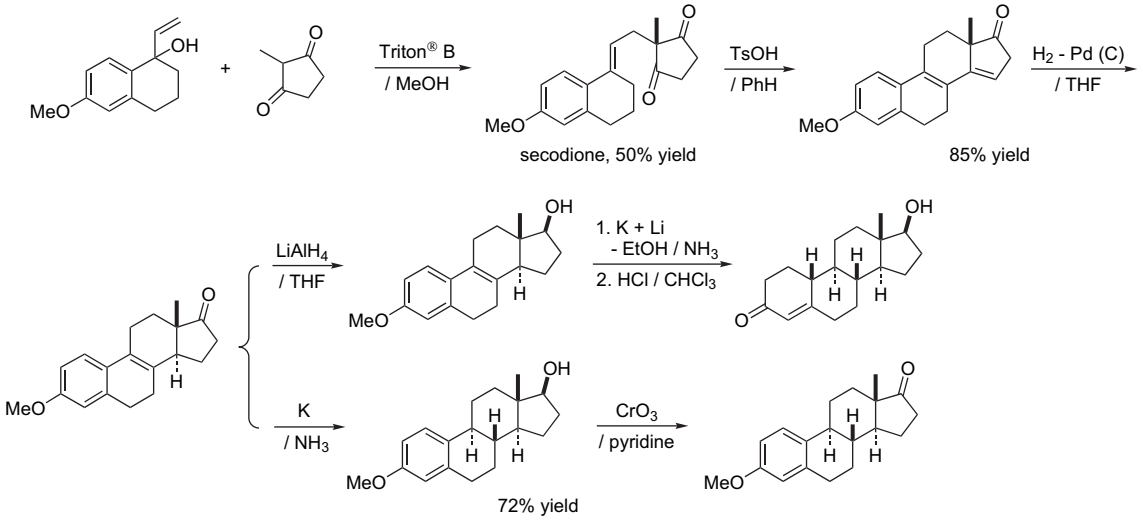
Scheme 2.

largely employed by different groups to synthesize steroid-type compounds.

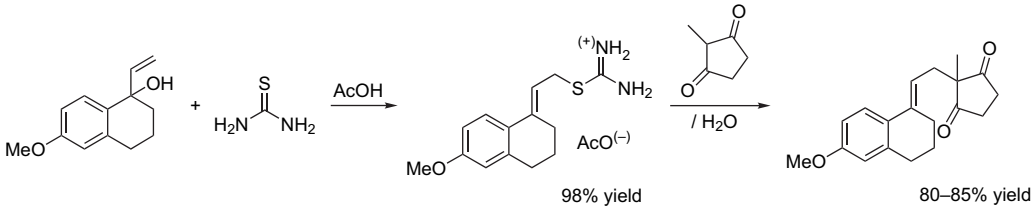
Ananchenko and Torgov extended this reaction to the preparation of estrone and 19-nor-testosterone by using methylcyclopentanedione as the D-ring precursor.[13] The thermodynamically disfavored trans-CD-ring junction was obtained by hydrogenation of the C(14)–C(15) double bond, while the *anti*-relation between the vicinal C(8) and C(9) atoms was established by a Birch-type reduction.[14] These significant results show that the configuration of the methyl group at the C(13) carbon center can induce the trans-*anti*-trans relative stereochemistry of the natural steroids (Scheme 3).

In parallel studies, this method was exploited by Merck Sharp and Dohme chemists to prepare 19-nor-testosterone[15] and a major oral contraceptive was elaborated from ethylcyclopentanedione by Wyeth Ltd.[16] Simultaneously, it was shown that the yield of the Torgov reaction could be improved by the preliminary formation of a thiouronium salt, as depicted in Scheme 4.[17]

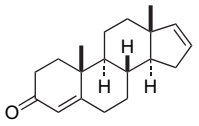
Most of the biological activity of steroids is strictly restricted to the natural enantiomer. The triterpenes, which are the precursors of cholesterol and the metabolization of which leads to various steroids, are present only as one enantiomer in Nature. In general, a loss of 50% of the activity results for racemic compounds. However, *ent*-steroids may have a different physiological activity from their natural enantiomer (*nat*-steroid).[18] To illustrate this difference of physiological behavior, (+)-androsta-4,16-dien-3-one was found to have a strong urine odor with an extraordinarily lower threshold of 1 ppb, whereas its enantiomer does not have any odor (Fig. 1).[19,20]



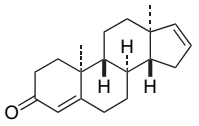
Scheme 3.



Scheme 4.



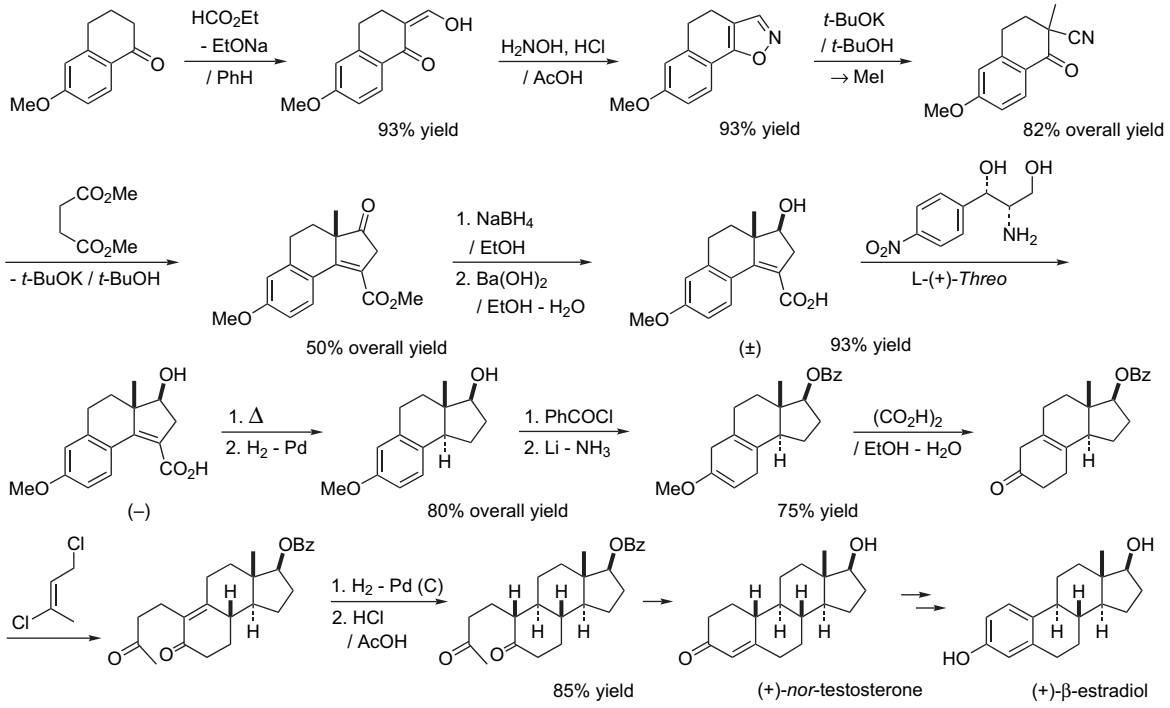
(+)-androsta-4,16-dien-3-one



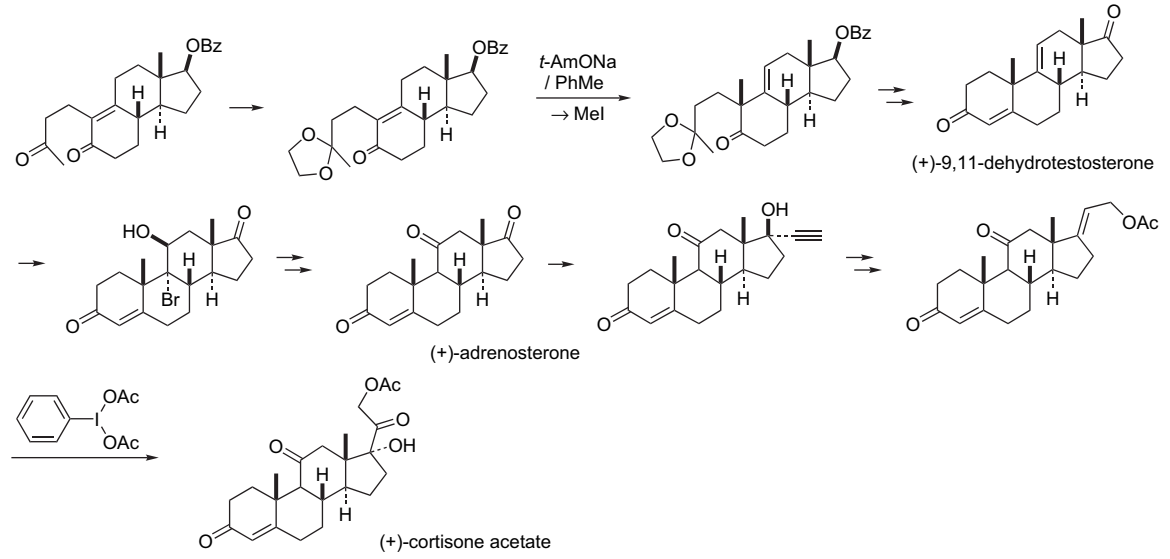
ent-androsta-4,16-dien-3-one

Figure 1.

To obtain steroids of the natural series, chemists first resolved hemiphthalates or hemisuccinates of *rac*-steroids[21,22] or carried out enzymatic resolutions,[22] but these strategies present the major disadvantage of losing half of the synthesized product. In consequence and for economic reasons, it seems preferable to perform the resolution as soon as possible in the synthesis using, for example, the acid function of a synthetic intermediate to separate both enantiomers. Based on this strategy, Velluz and co-workers from Roussel-Uclaf described in 1960 the first enantioselective synthesis of (+)-nor-testosterone. The linear approach reported by Johnson[23] and applied by Banerjee[24] involved a tricyclic acid, which could be resolved by (+)-(1*S*,2*S*)-1-*p*-nitrophenyl-2-aminopropane-1,3-diol. The subsequent steps gave rise to (+)-nor-testosterone and also to (+)-β-estradiol (Scheme 5), (+)-9,11-dehydrotestosterone, (+)-adrenosterone, and (+)-cortisone (Scheme 6).[25] This sequence constitutes the first total synthesis of natural steroids on an industrial scale.



Scheme 5.



Scheme 6.

Over the last few years, several review articles[26] based on synthetic approaches to different classes of steroids including vitamin D-like structures have emerged in the area of steroid chemistry, but these usually consider a single aspect such as the construction of the aliphatic side chain,[27] the obtaining of the *trans*-hydrindane ring,[28] its elaboration through C-ring closure as a key step,[29] the preparation of enantiomeric steroids,[18] steroid synthesis involving intramolecular cycloadditions or transition-metal-catalyzed reactions[30] and, finally, various approaches to vitamin D synthesis.[31] In the present review, the major approaches toward enantioselective steroid synthesis, the corresponding key steps of which are classified according to the method used to introduce the chirality, are explored. Synthetic routes, involving functional-group transformations of metabolic or degradation precursors of natural steroids, will not be covered by this review.

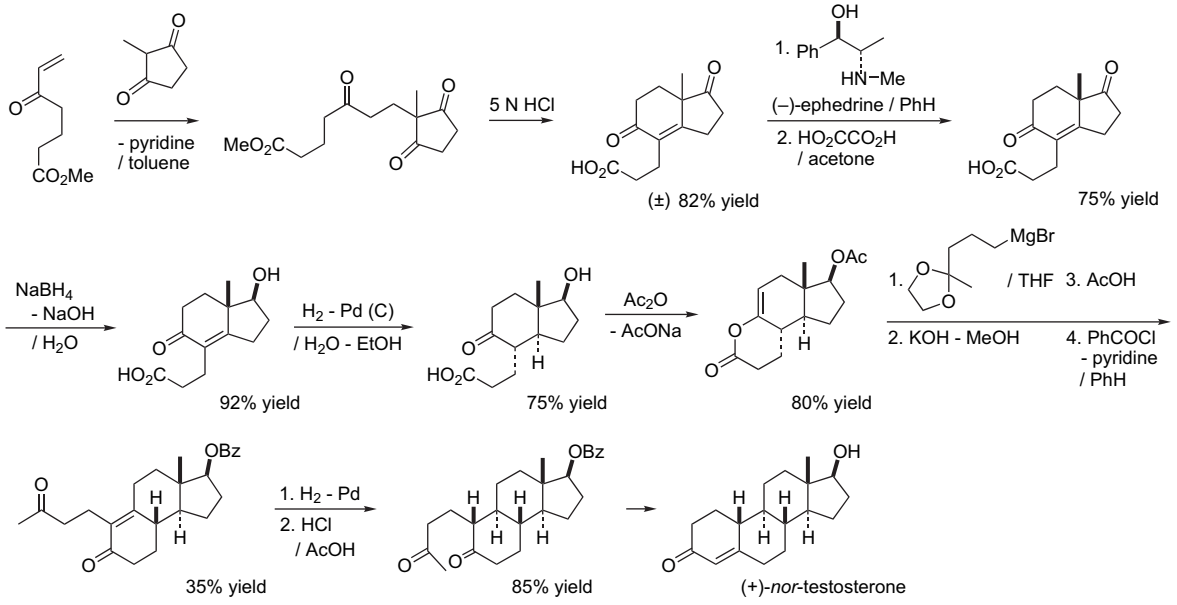
2. Chemical resolution of chiral synthetic intermediates

2.1. By recrystallization of diastereomeric salts

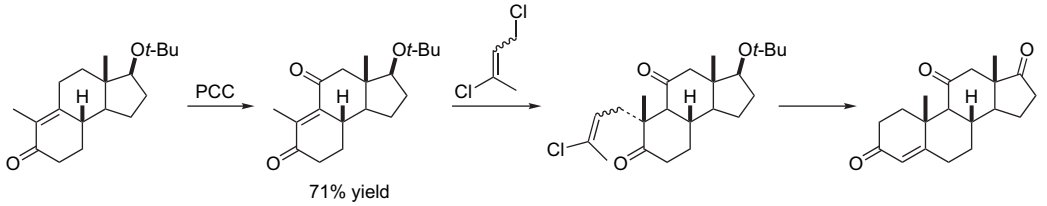
To render their synthesis convergent, chemists from Roussel-Uclaf have prepared earlier in the sequence a new optically pure bicyclic acid via a tandem conjugate addition–Robinson annulation and its resolution with (−)-ephedrine. A significant result was obtained with the diastereoselective hydrogenation of this acid that led to the CD-bicyclic system with a trans-ring junction. The formation of an intermediate δ-lactone followed by its reaction with the Grignard reagent of 2-(2-bromo-ethyl)-2-methyl-[1,3]dioxolane, according to the Fujimoto–Belleau reaction,[32] allowed the construction of the B-ring. A subsequent cyclization through aldol condensation completed the synthesis (Scheme 7).[33] Adrenosterone also was accessible by reductive alkylation of the tricyclic enedione with the Wichterle reagent and cyclization (Scheme 8).[34]

An elegant strategy was elaborated by the Merck group involving resolution of a synthetic intermediate without loss of product. The secodione from the Torgov reaction could be selectively reduced to a ketol and its hemisuccinate subjected to an optical resolution with quinine. The dextrorotatory enantiomer was recycled after saponification and oxidation of the hydroxyl group in position C(17) (Scheme 9).[35]

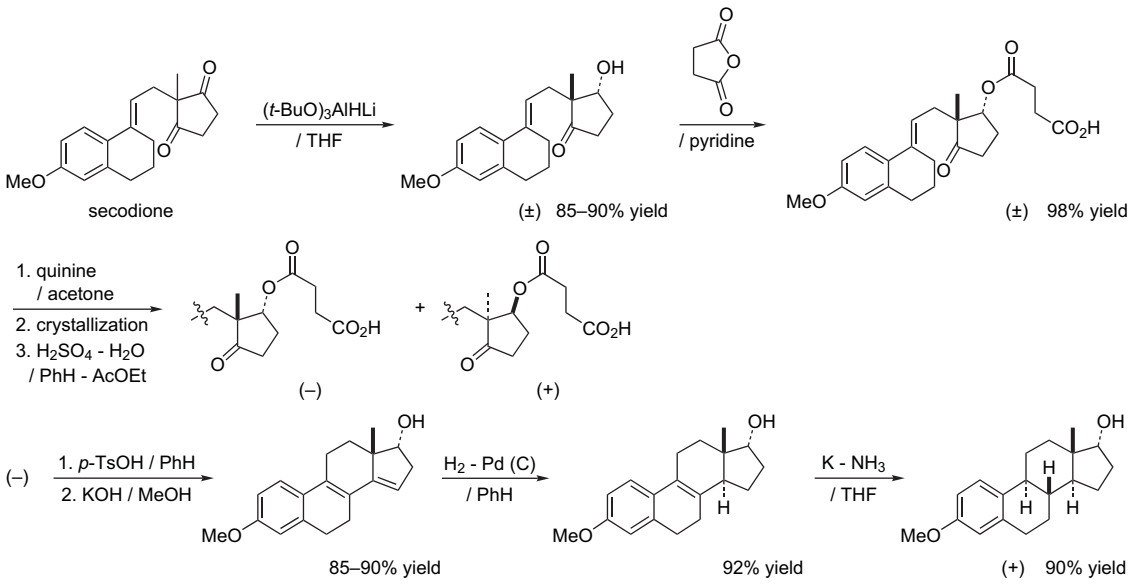
Hajos and Parrish reported the synthesis of the optically active (−)-17β-hydroxy-des-A-androst-9(10)-in-5-one, easily accessible from the indenol via a Robinson annulation of methylcyclopentanedione with methylvinylacetone followed by a selective carbonyl reduction. The corresponding phthalate was resolved through diastereomeric salt formation with brucine. Construction of the key BCD-tricyclic intermediate[36] used in the synthesis of steroids was realized as shown in Scheme 10.[37]



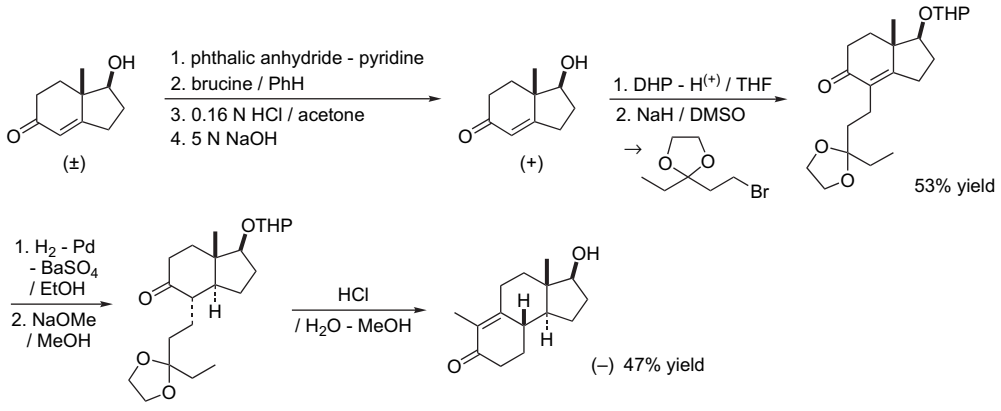
Scheme 7.



Scheme 8.



Scheme 9.



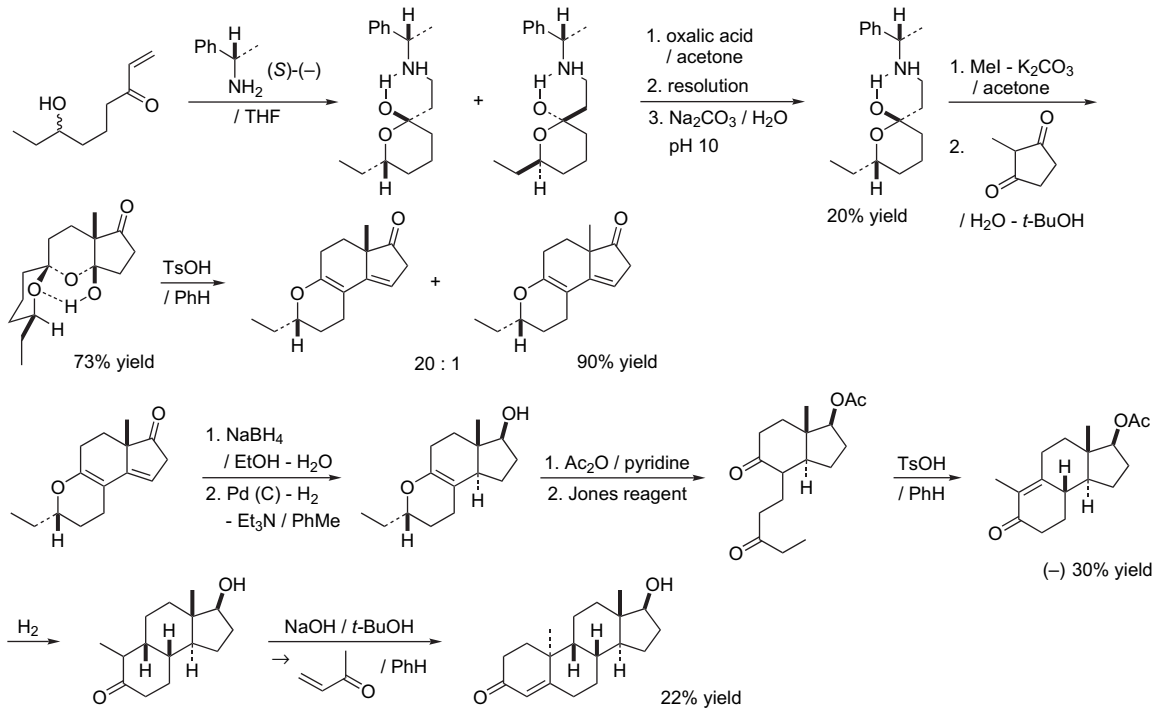
Scheme 10.

Saucy and Borer could easily prepare (−)-17β-hydroxy-des-A-androst-9-en-5-one, an optically pure tricyclic hydroxyketone used as a precursor of 9β,10α-testosterone. The initial resolution was ensured by a conjugate addition of (*S*)-(−)-α-methylbenzylamine to a vinyl ketone obtained by the addition of vinylmagnesium chloride to 5-decanolide.[38] The resulting spiroheterocyclic Mannich adduct was converted into the BCD-tricyclic system after successive transformations comprising (a) its reaction with 2-methyl-cyclopentane-1,3-dione followed by acidic treatment, (b) hydrogenation of the transient diene that established the trans-ring junction of the hydrindane, (c) hydration and oxidation of the enol ether, and (d) aldol cyclocondensation of the resulting diketone. The final hydrogenation of the enone motif and the annulation of the tricyclic ketone with methyl vinyl ketone completed the synthesis of 9β,10α-testosterone (Scheme 11).[39]

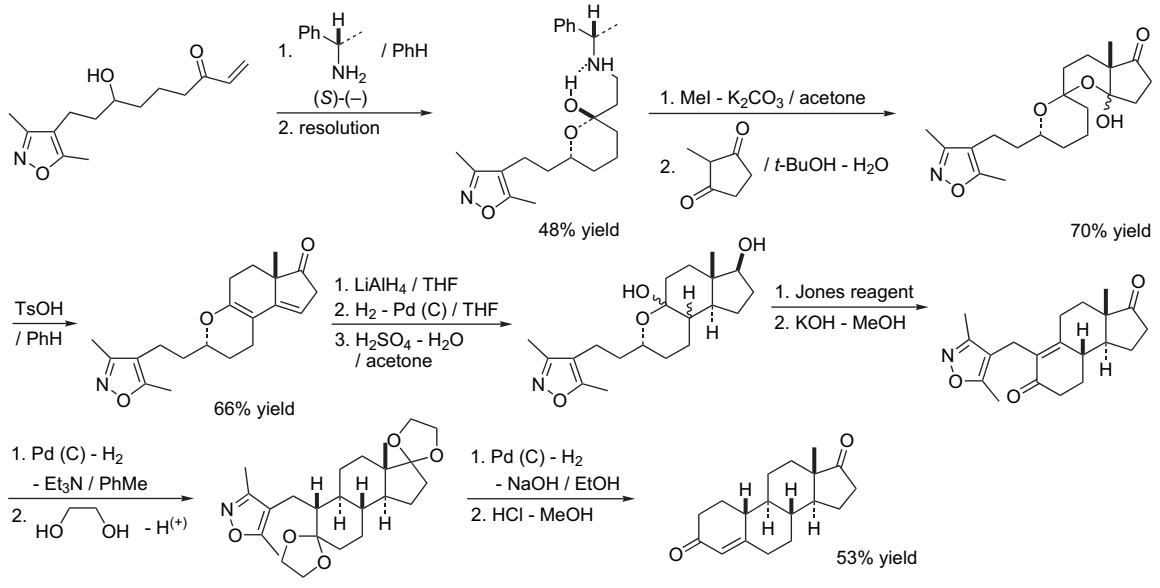
Subsequently, a similar strategy was applied to the resolution of a vinyl ketone intermediate conveniently substituted by a linear side chain including an isoxazole moiety. Under basic conditions, the isoxazole annulation reaction developed by Stork[40] allowed a direct access to (+)-estr-4-ene-3,17-dione-type steroids (Scheme 12).[41]

By contrast, the optical resolution was performed at an early stage on the acid phthalate derivative of a hydroxy nitrile intermediate using (*R*)-(+)-α-methylbenzylamine. The resulting optically active lactone was readily converted into the desired Mannich base from the corresponding vinyl ketone in a few steps. Its condensation with 2-methyl-1,3-cyclopentanedione in refluxing toluene/acetic acid afforded predominantly the expected ketol epimer. The dehydroxylated enedione adduct cyclized to (+)-3-methoxy-1,3,5(10),9(11)-estratetraen-17-one according to the sequence of Smith and co-workers[42] in which installation of the trans-fused ring junction required a diastereoselective hydrogenation over palladium on carbon of the C-8 substituted 17β-hydroxy enone intermediate. Then, a reoxidation and an acid-promoted cyclization–dehydration sequence completed the approach (Scheme 13).[43]

During the convergent synthesis of (+)-3-methoxy-1,3,5(10)-estratrien-11,17-dione, Oppolzer and co-workers resolved



Scheme 11.

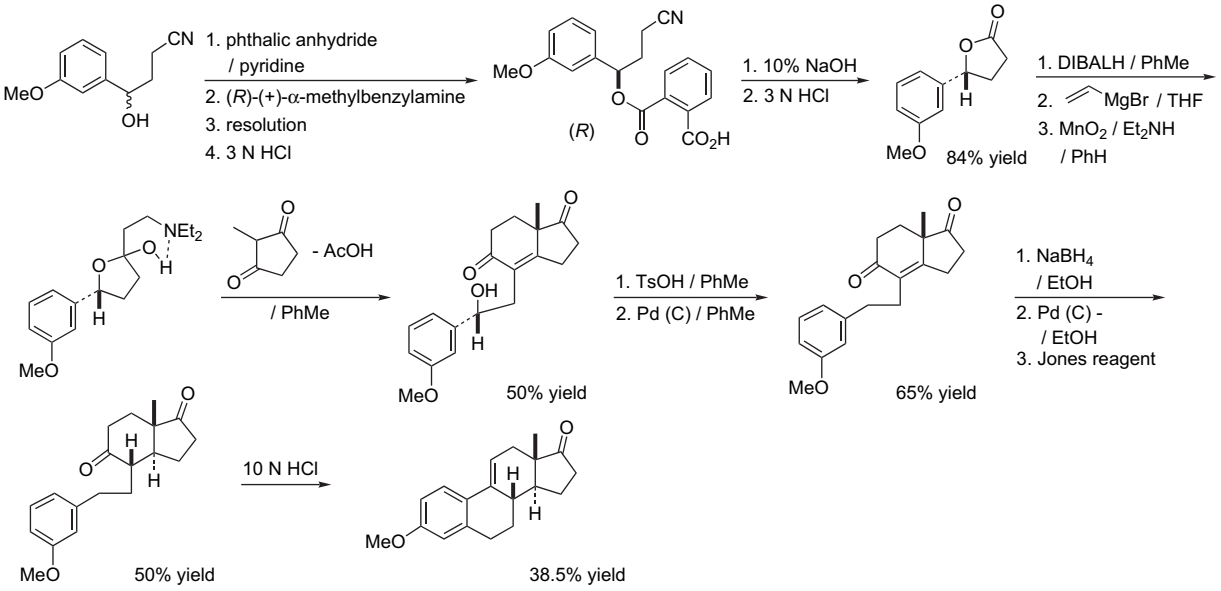


Scheme 12.

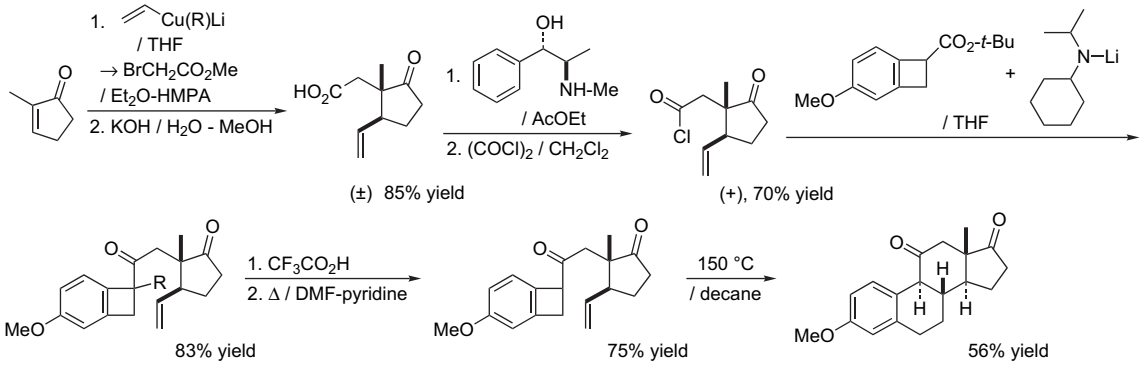
a keto acid intermediate by crystallization of the related (+)-ephedrine salt. The starting keto acid was obtained by sequential conjugate addition of lithium 3,3-dimethylbutynylvinylcuprate to 2-methyl-2-cyclopentenone and enolate alkylation with methyl bromoacetate. The enantiomerically pure vinylcyclopentane subunit was coupled with a benzocyclobutenecarboxylic ester by C-acylation and readily engaged in a thermal intramolecular Diels–Alder cycloaddition with a transient reactive *o*-quinodimethane coming from the ring opening of the benzocyclobutene motif (Scheme 14).[44]

Oppolzer and Roberts described a concise synthesis of (+)-estradiol involving a regioselective alkylation of 5-cyano-1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide by an alkyl iodide derived from the previous optically active keto acid fragment, and a thermal SO_2-extrusion/cycloaddition sequence. Further transformations led to (+)-estradiol with a global yield of 42% (Scheme 15).[45]

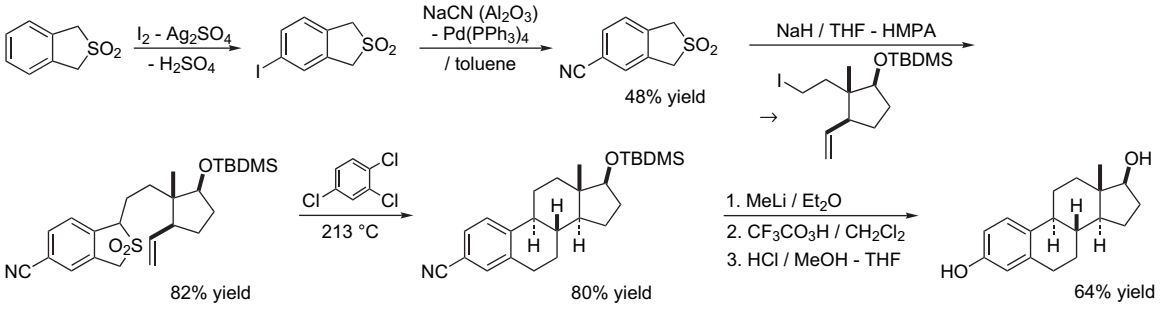
An alternative approach used to synthesize enantiomerically enriched 19-nor-steroids oxidized in position 11 was proposed by Daniewski. Michael addition of methylcyclopentanedione to methyl chloroacrylate and subsequent transformations gave access to *rac*-2-methyl-2-(β-acetoxy-β-carboxyethyl)cyclopentane-1,3-dione, which could be resolved by means of (−)-α-phenylethylamine. In order to set



Scheme 13.



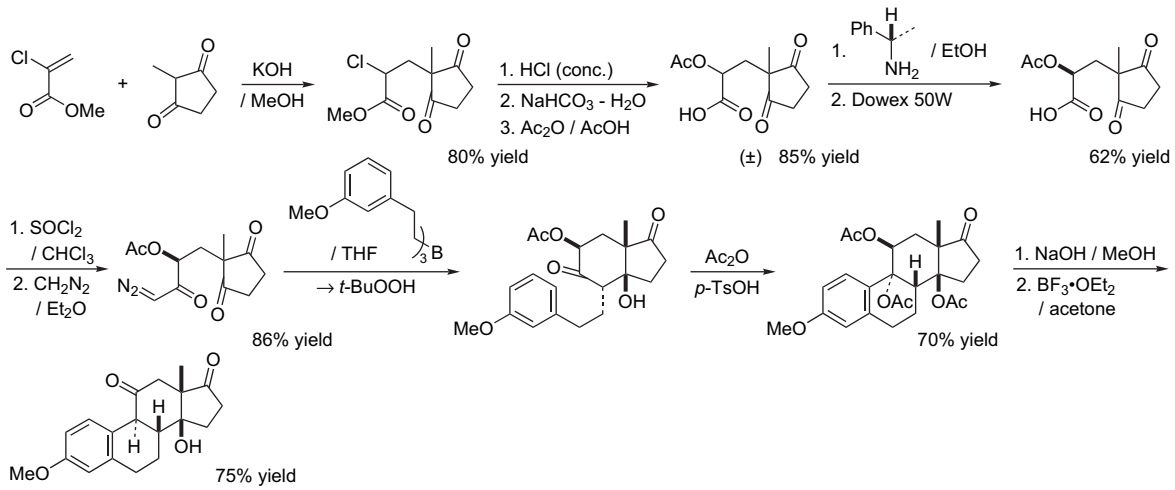
Scheme 14.



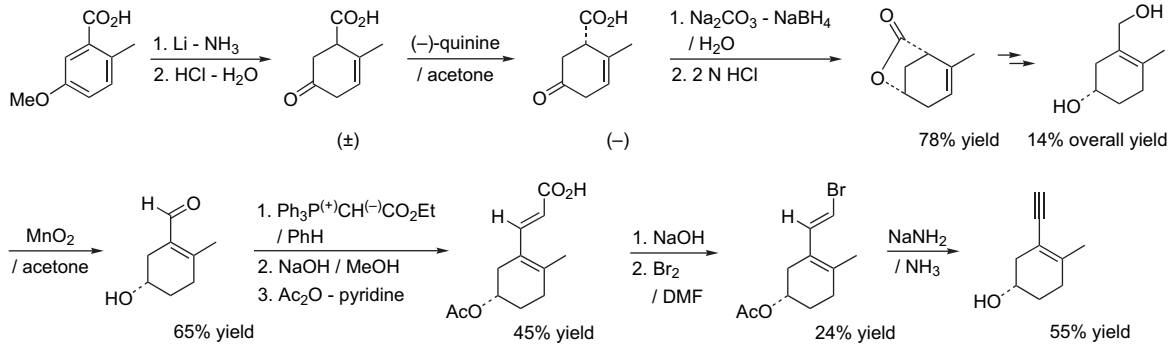
Scheme 15.

up the C-ring, Daniewski converted the starting acid into a diazo ketone and coupled it with a trialkylborane. The boron compound attacked the diazo ketone only from the less hindered side and a concerted and stereospecific 1,2-shift of one phenylethyl group accompanied by nitrogen elimination yielded the tricyclic secodione with a cis-ring junction. Thus, the latter underwent a cyclization reaction upon treatment with Ac_2O/*p*-TsOH leading to the 11-oxidized 19-norsteroid skeleton (Scheme 16).[46]

In their pioneer work on vitamin D and its derivatives, Lythgoe and co-workers achieved the preparation of an optically active hydroxy enyne, precursor of the A-ring of vitamins D. The key steps involved resolution of the racemic keto-acid induced by (−)-quinine and reduction of the (−)-enantiomer to the intermediate lactone, from which the diol was accessible. The enyne was obtained by dehydrohalogenation of the ω-bromodiene with $NaNH_2$ in ammonia (Scheme 17).[47]



Scheme 16.



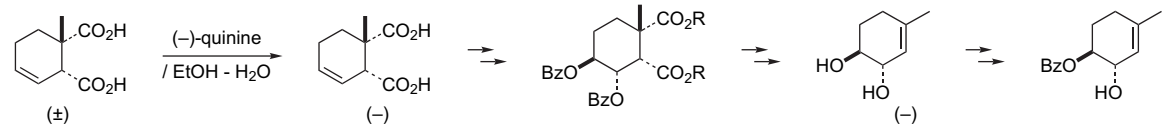
Scheme 17.

The future C-ring was elaborated from 1-methylcyclohex-3-ene 1,*cis*-2-dicarboxylic acid in enantiomerically pure form by resolution with (−)-quinine and converted into the monoprotected diol, as illustrated in Scheme 18.[48] In parallel, a precursor of the side chain was prepared in two steps starting from the citronellonitrile. Both fragments were subjected to a stereospecific Johnson–Claisen [3,3] rearrangement, which facilitated the introduction of the side chain and the control of the stereochemistry in position C(17). A second Claisen-type rearrangement using the Eschenmoser procedure ensured the stereochemistry of the C(14) center. Finally, the D-ring was revealed through a Dieckman condensation and further conventional transformations furnished the 9α-chloro ketone (Scheme 19).[49,50]

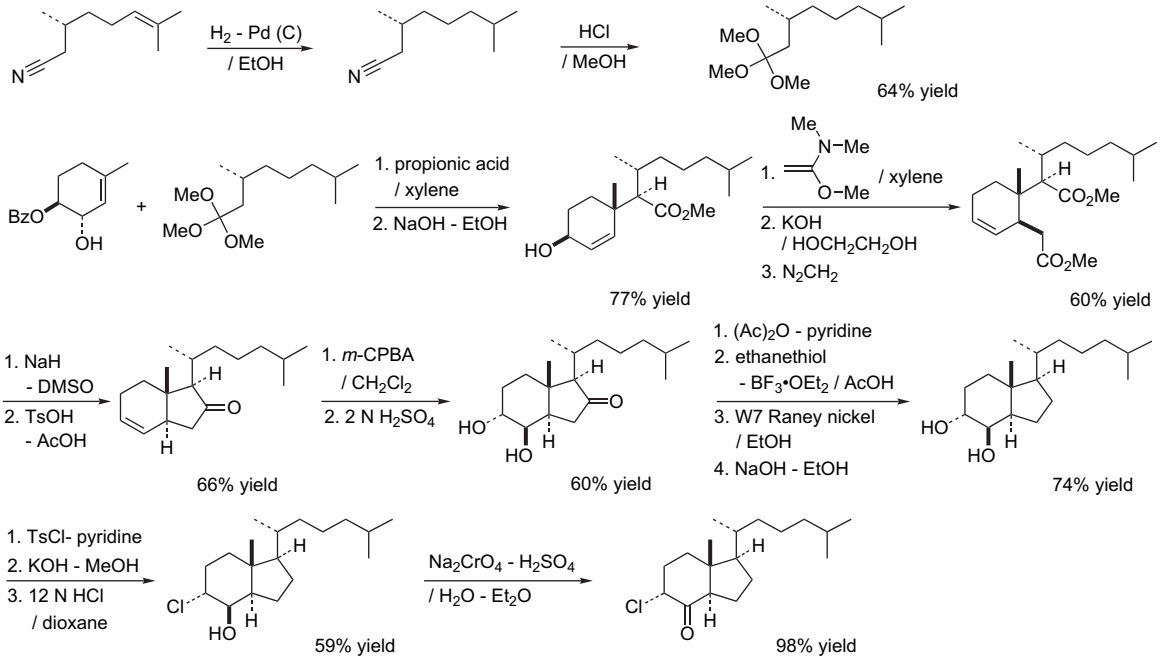
With the enyne and the *trans*-hydrindane building blocks in hand, Lythgoe and co-workers achieved the synthesis of precalciferol in only three steps. The requisite trienic system was assembled by coupling the 9α-chloro-des-AB-cholestan-8-one with the lithium derivative of the silyl-protected (1*S*)-3-ethynyl-4-methylcyclohex-3-en-1-ol to give the chlorohydrin intermediate, followed by treatment with bis-(ethylenediamine)chromium(II) and semi-hydrogenation of the dienyne system (Scheme 20).[51]

The same sequence carried out with 1-ethynyl-2-methyl-3,5-bis(trimethylsilyloxy)cyclohexene furnished 1α-hydroxyprecalciferol, which was converted in situ into 1α-hydroxyvitamin D_3 through a thermal [1,7] hydrogen sigmatropy and an isomerization of the trienic system (Scheme 21).[52]

In 1978, Lythgoe and co-workers provided a more straightforward route to reach the trienic system of vitamin D utilizing a dienic alcohol as an A-ring synthon, which could be easily coupled to the Windaus–Grundmann ketone.[53] First of all, the authors achieved the synthesis of the optically active diene diol by resolution of the racemic *trans*-cyclohexenedicarboxylic acid with cinchonidine.[54] The approach to such a fragment, involving unsaturated lactone formation, conversion into diol, and sulfoxide thermolysis,[55] was



Scheme 18.



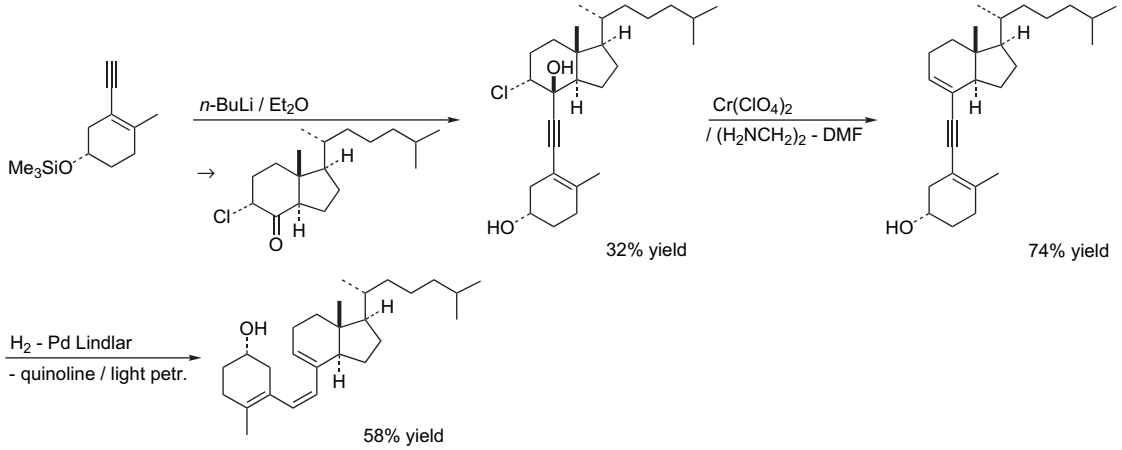
Scheme 19.

revealed to be quite long, not very attractive and not competitive enough, compared to the degradation of vitamin D (Scheme 22).[56]

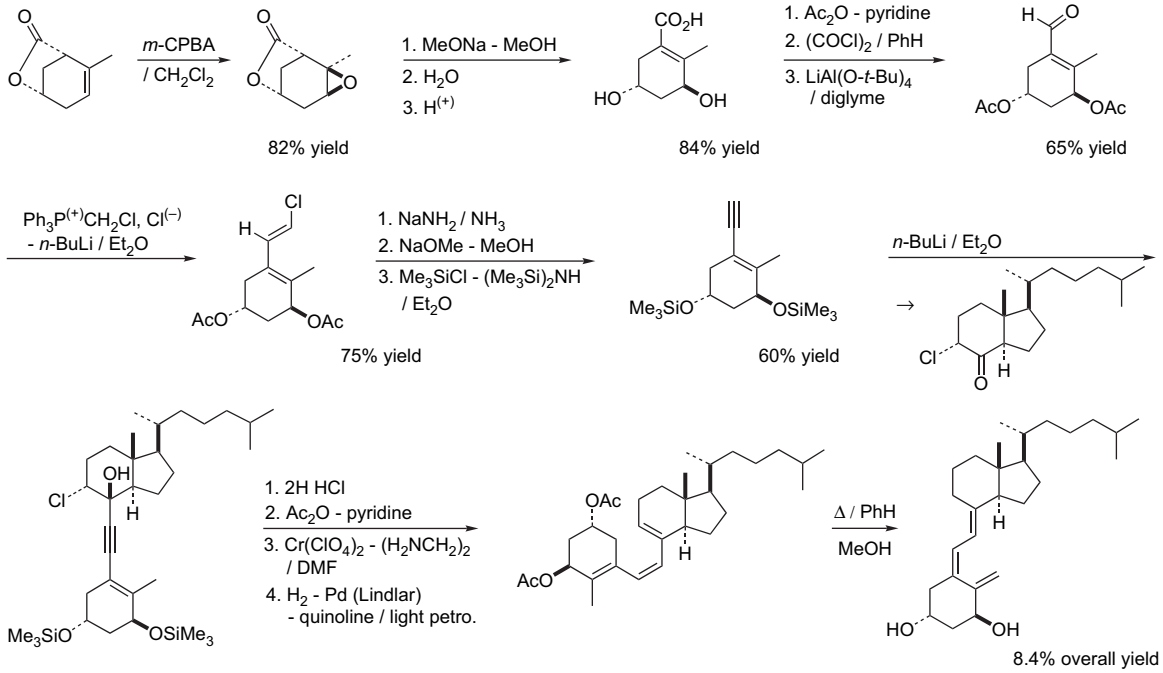
By virtue of Linstead's work on the resolution of β-methylglutaric acid with cinchonidine,[57] Lythgoe could prepare an optically active γ-lactone, from which he proposed a second synthesis of the indanic CD-bicyclic system of vitamin D. A Claisen rearrangement with an optically active allyl alcohol and the γ-lactone-derived cyclic orthoester set up the asymmetric center C(13) and the rest of the synthesis followed the protocol previously described and standard pathways to afford the optically active Inhoffen–Lythgoe diol. Then, the introduction of the side chain through a coupling reaction between the primary tosylate and a Grignard reagent and its functionalization with $Hg(OAc)_2$–$H_2O/NaBH_4$ furnished the des-AB vitamin D_3 (Scheme 23).[58]

Thereafter, the Windaus–Grundmann ketone and the lithio anion of the allylic phosphine oxide derived from the dienic alcohol underwent a Wittig–Horner reaction, leading directly to the trienic system with the correct geometry (Scheme 24).[59]

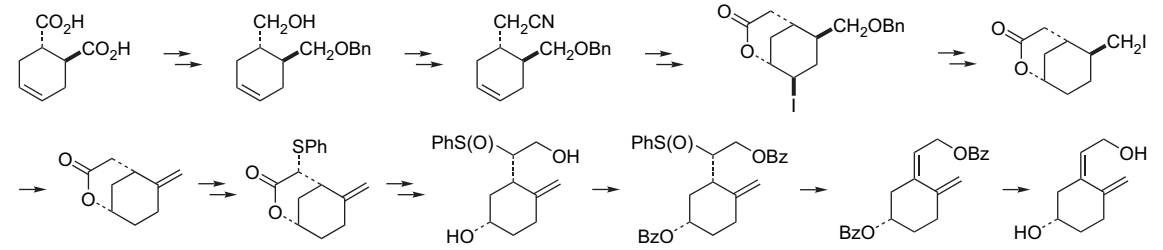
In parallel work, Kocienski and co-workers proposed that the roles of the two fragments be reversed by creating a nucleophilic center at the C(8)-position of the hydrindane system, which should interact with the A-ring aldehyde, coming from the oxidation of the previous dienic alcohol synthon. To make this coupling accessible, the authors prepared the sulfone, the lithio anion of which, shown in Scheme 25, reacted with the aldehyde and gave the Julia olefination adduct. Reduction with a lithium mercury amalgam followed by removal of the benzoyl group generated the trienic part of the vitamin D_4 (Scheme 25).[60]



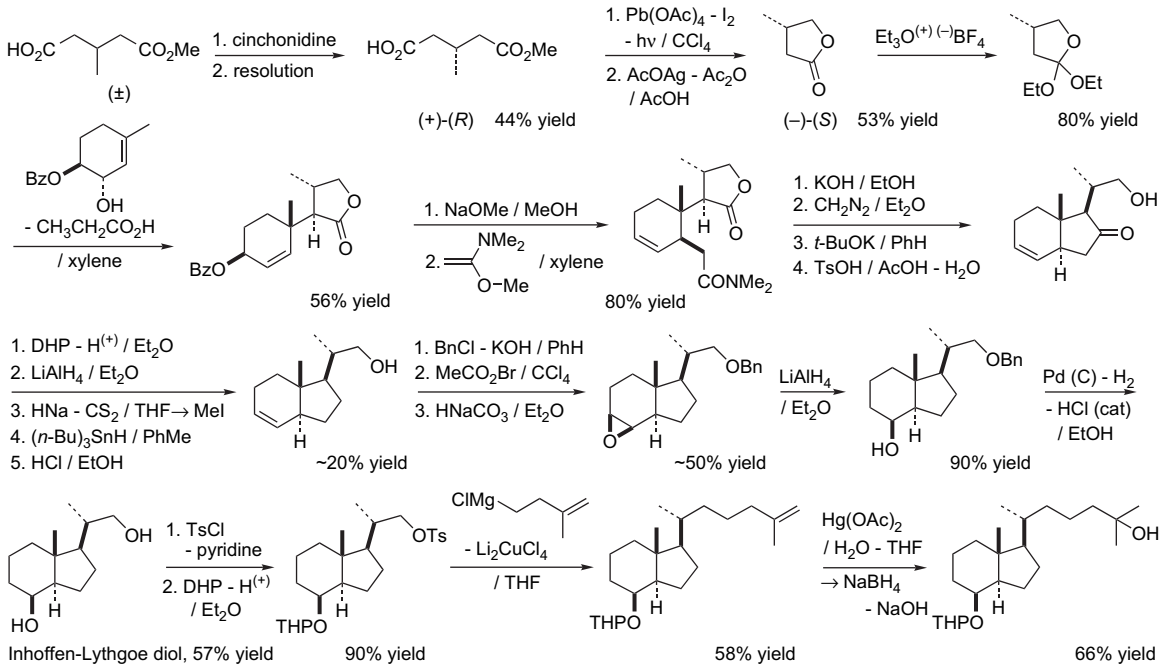
Scheme 20.



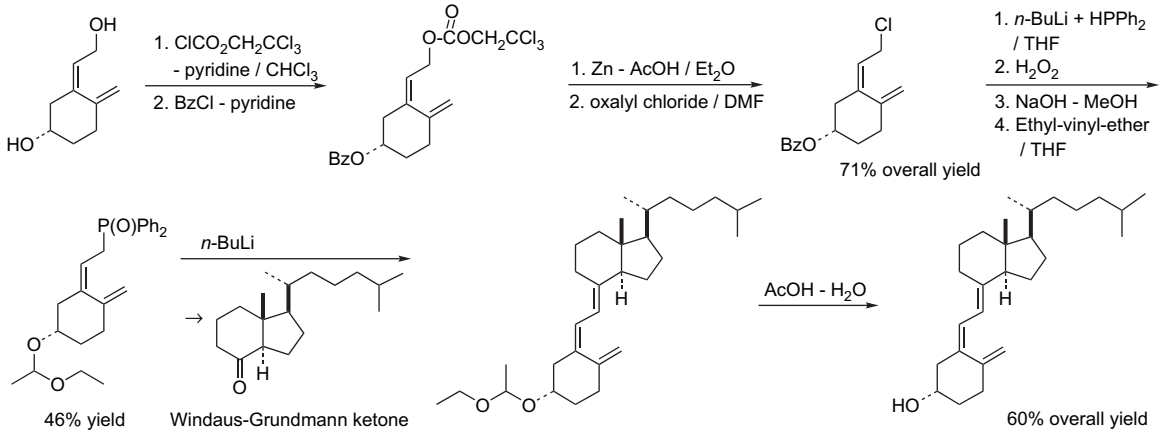
Scheme 21.



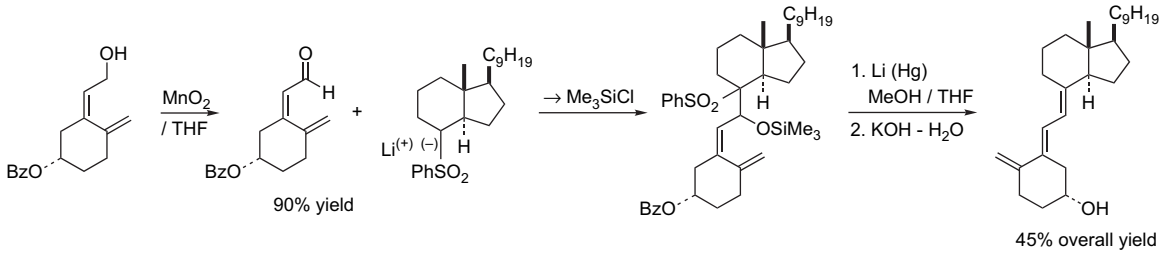
Scheme 22.



Scheme 23.

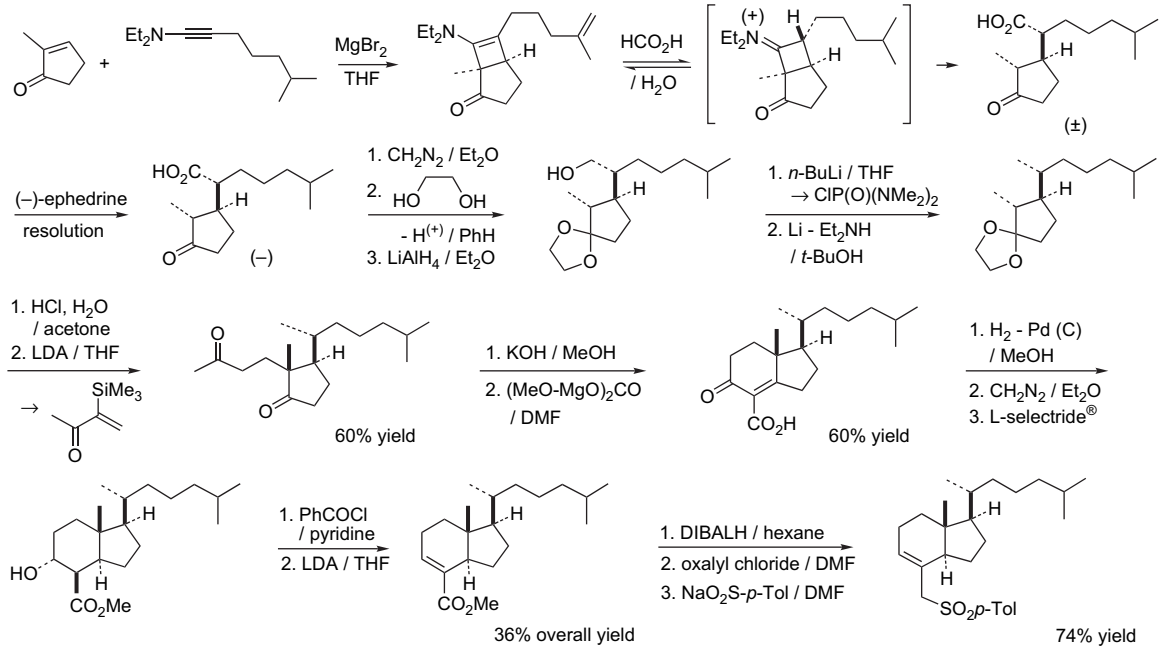


Scheme 24.

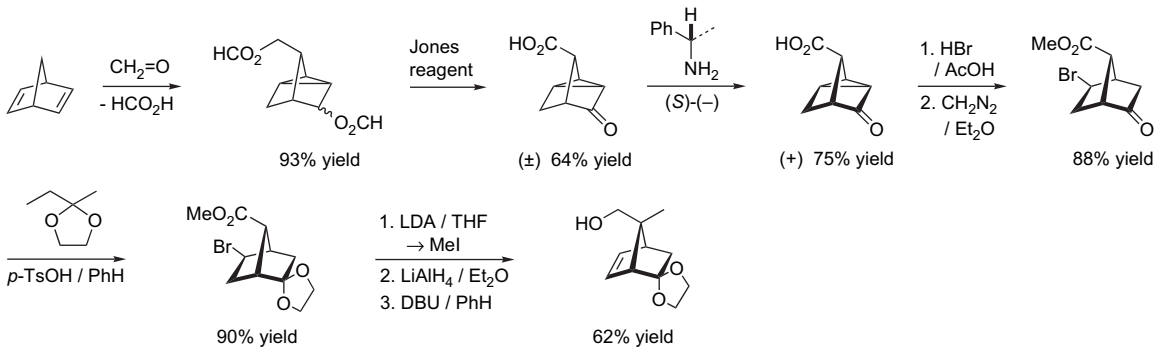


Scheme 25.

In addition, this research group has reported an access to 1α-hydroxyprecalciferol utilizing a CD-bicyclic allylic sulfone obtained by degradation of a cholesterol derivative.[61] A totally synthetic route of the same synthon was developed by Ficini and co-workers in 1983. One of the key reactions was the Lewis acid-catalyzed [2+2] cycloaddition of an ynamine to methylcyclopentenone. The thermodynamic hydrolysis of the immonium cation released the side chain with the desired stereochemistry at C(13). A resolution of the resulting acid with (−)-ephedrine made this approach possible in the natural series. 8-*p*-Tolylsulfonylmethyl-des-AB-cholest-8-ene, a known precursor of 1α-hydroxyvitamin D_3, could be prepared through Robinson annulation generating the C-ring and catalytic reduction of the α,β-unsaturated keto-acid establishing the CD trans-junction, as depicted in Scheme 26.[62]



Scheme 26.



Scheme 27.

A structurally interesting enantiopure bicyclic keto acid has been exploited in efficient syntheses of tetracyclic and seco-B steroids by Grieco and Trost, respectively. Its preparation and resolution with (*S*)-(−)-α-methylbenzylamine were reported by Corey, who used it as a key intermediate in the elaboration of prostaglandins.[63] Grieco suggested pertinent functional modifications including the stereoselective alkylation of the methyl ester enolate, later applied in the total synthesis of steroids (Scheme 27).[64]

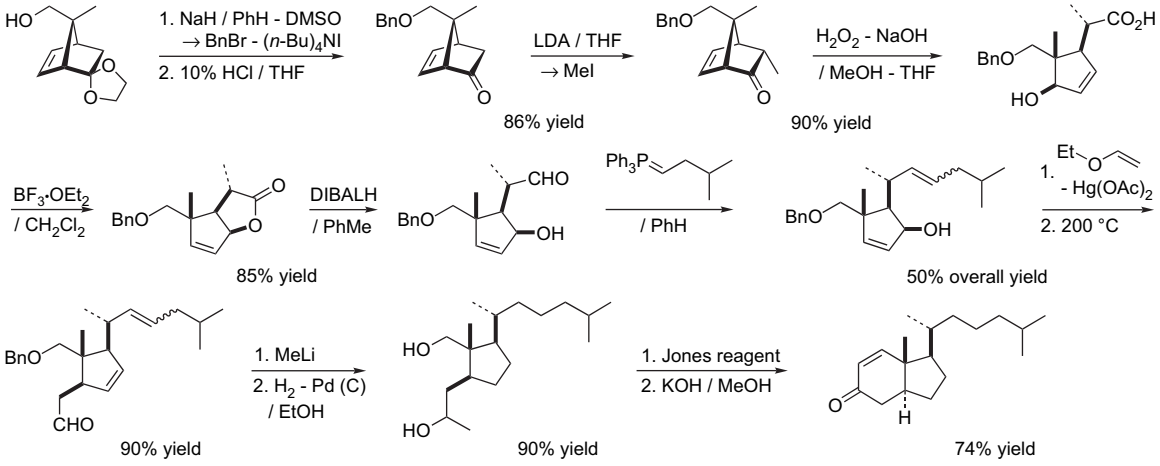
Thus, Grieco achieved the conversion of this bicyclo[2.2.1]-heptane derivative into (+)-des-AB-cholest-11-en-9-one, a known precursor of tachysterol$_3$ and precalciferol$_3$. First, the compound was transformed into a key bicyclic lactone by sequential Baeyer–Villiger oxidation and BF_3-catalyzed allylic transposition. The hydroxyl group at C(16) provided a handle for establishing the stereochemistry at C(14) via a 1,3-chirality transfer involving a [3,3]-Claisen sigmatropic rearrangement (Scheme 28).[65]

One year later, an approach to the synthesis of DL-estrone was reported in which Grieco examined the stereospecific alkylation of the enolate derived from the unsaturated bicyclic ketal ester with 2-(4-methoxybenzocyclobutenyl)ethyl iodide. Upon thermolysis, the corresponding *o*-quinodimethane intermediate underwent intramolecular cycloaddition and led to the desired steroid (Scheme 29).[66]

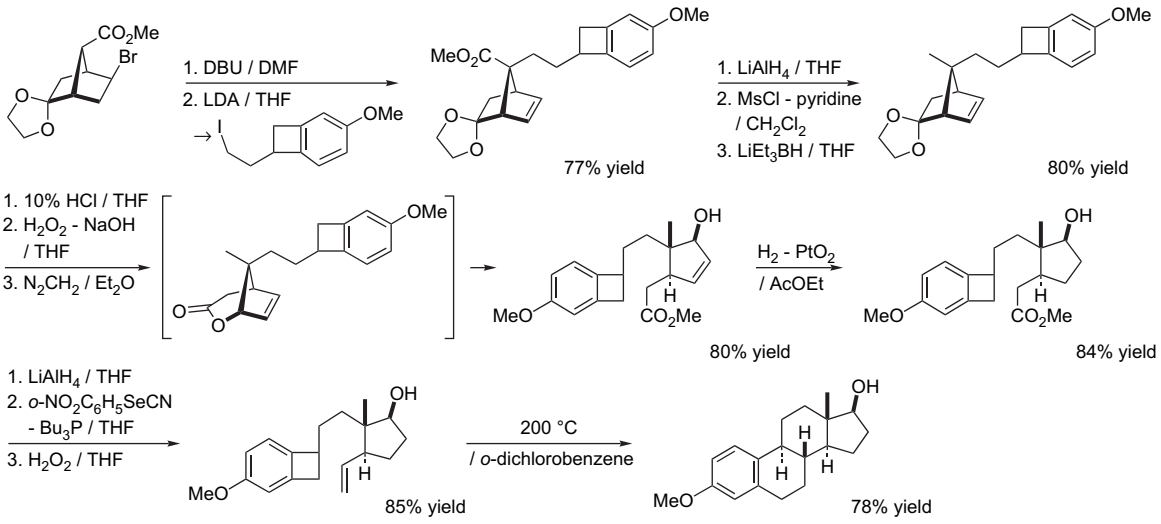
In parallel, Trost was interested in preparing the Inhoffen–Lythgoe diol starting from the optically pure bicyclic hydroxy ketal, as indicated in Scheme 30. The 1,3-chirality transfer process used for the elaboration of the CD trans-junction was almost similar to the preceding Grieco's protocol. Then, an advanced synthon of the Windaus–Grundmann ketone could easily be obtained from the Inhoffen–Lythgoe diol after different functional-group manipulations.[67]

2.2. By chromatographic separation of diastereomers

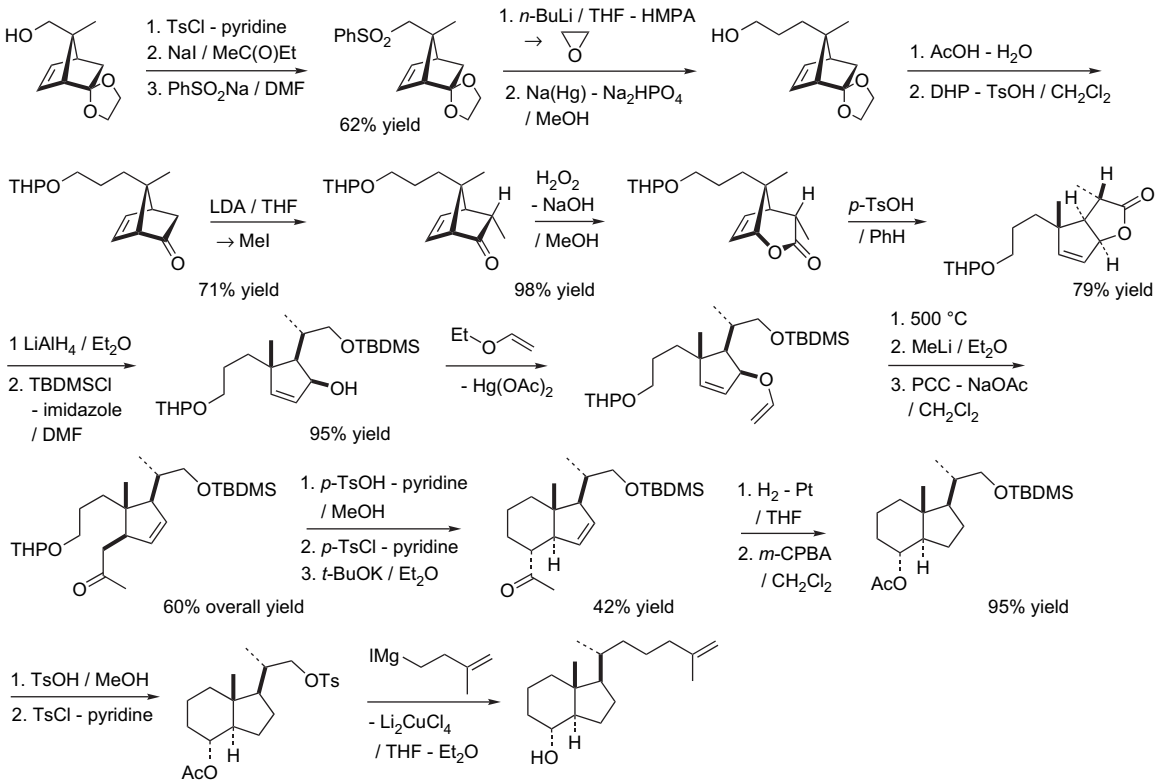
Besides the diastereomeric salt crystallization method, the resolution of enantiomers of chiral synthetic intermediates is also possible by derivatization to diastereomers and separation by chromatography. To illustrate this method, Jiang and Covey reported an efficient synthesis of *ent*-cholesterol, the chirality of which originated from the enantiomerically pure sterol D-ring containing the side chain, and the other sterol C-, B- and A-rings were subsequently elaborated. Based on published studies, the D-ring synthon was formed via high diastereoselective intramolecular cyclopropanation of an α-diazoester catalyzed by a copper(II) complex, and the side chain was introduced by conjugate addition of 4-methylpentylmagnesium bromide in the presence of CuI to the β-keto ester with retention of configuration, ensuring the proper relative stereochemistry at C(17) and C(20).[68]



Scheme 28.

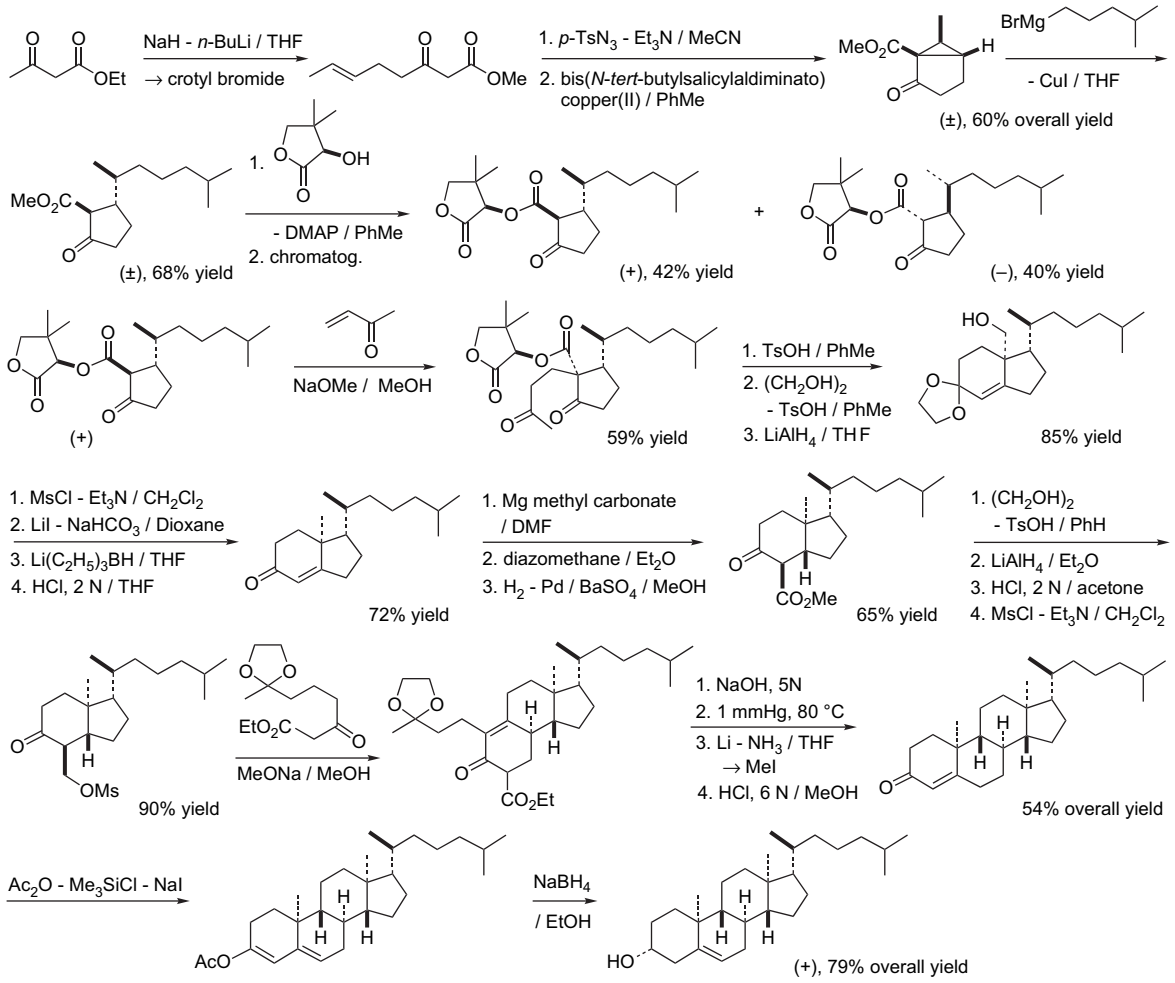


Scheme 29.



Scheme 30.

After transesterification with (*R*)-(+)-pantolactone, each diastereoisomers were easily separated by chromatography, and the dextrorotatory adduct was then engaged in a step-by-step Robinson annulation reaction with methyl vinyl ketone that gave rise to the related hydrindenone. Michael addition carried out at 0 °C guaranteed a total control of the stereoselectivity at the C(13) chiral center. Subsequent methoxycarbonylation at C(8) and hydrogenation of the double bond using 5% $Pd/BaSO_4$ gave the *trans*-hydrindanone as the unique product. The remaining B and A sterol rings were elaborated by cyclocondensation of a mesylate intermediate with ethyl 3,7-dioxo-octanoate mono ethylene ketal, the C(19) methyl group was introduced selectively via reductive alkylation of the enone functionality, and further transformations then afforded (−)-*ent*-cholesterol (Scheme 31).[69]

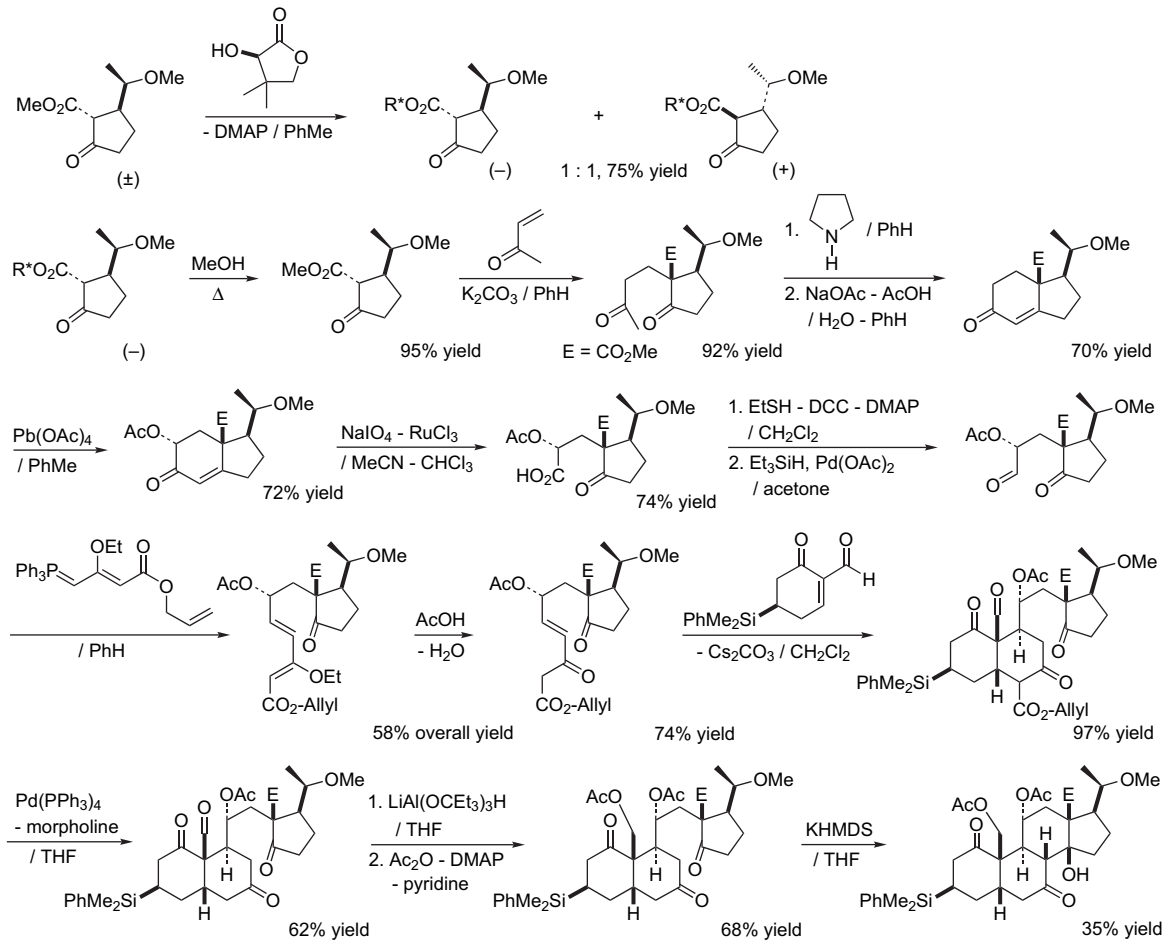


Scheme 31.

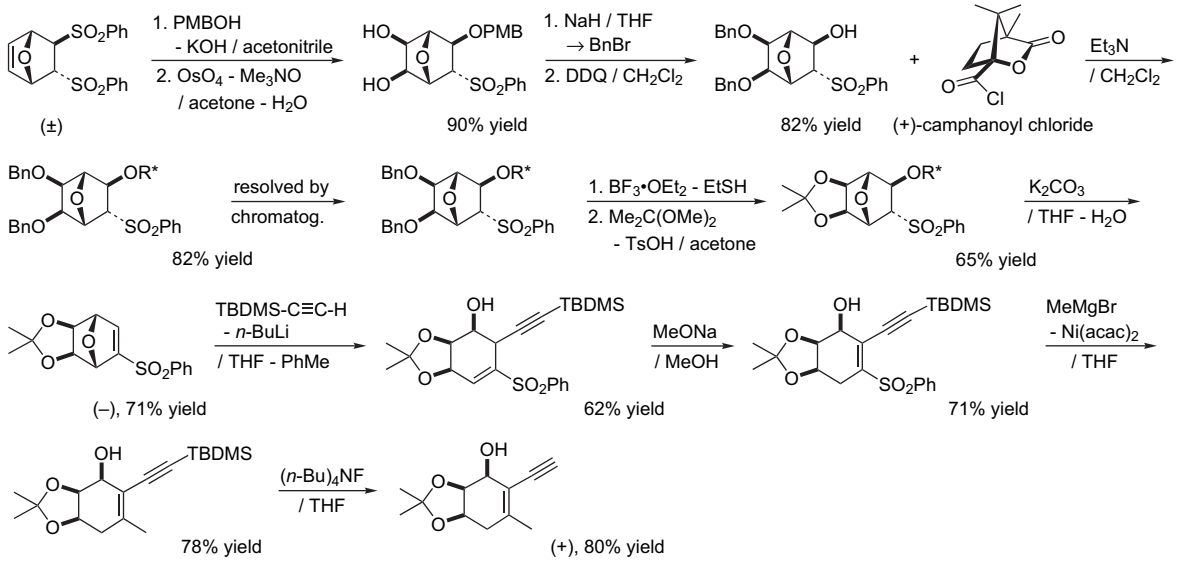
Deslongchamps has developed an anionic polycyclization procedure that allowed the preparation of advanced tetracyclic 14-β-hydroxysteroids related to batrachotoxin and ouabain with complete control of the stereochemistry. The reaction sequence involved the formation of a novel Nazarov-type reagent containing the D-ring and reaction of its enolate with an unsaturated β-keto aldehyde A-ring precursor. The introduction of chirality into the Nazarov intermediate was achieved by the use of (*R*)-(−)-pantolactone as a good chiral auxiliary and separation of the resulting diastereomers of the β-keto ester D-ring precursor according to Covey's work previously reported (Scheme 32).[70]

In 1998, an approach to an enantiopure A-ring enyne synthon for vitamin D_3 analogs starting from a 7-oxanorbornenic disulfone was published. Arjona and co-workers showed that the derived racemic β-hydroxy sulfone could be resolved to pure enantiomers via diastereomeric ester formation with the use of (+)-camphanoyl chloride as a chiral derivatizing agent. After separation of both compounds on silica gel and elimination of the camphanol group of the (−)-diastereomer under basic conditions, the resulting vinyl sulfone was subjected to an alkylative cleavage of the oxygen bridge with lithium acetylide. Final vinyl sulfone isomerization and substitution of the sulfone functionality by a methyl group liberated an A-ring analog (Scheme 33).[71]

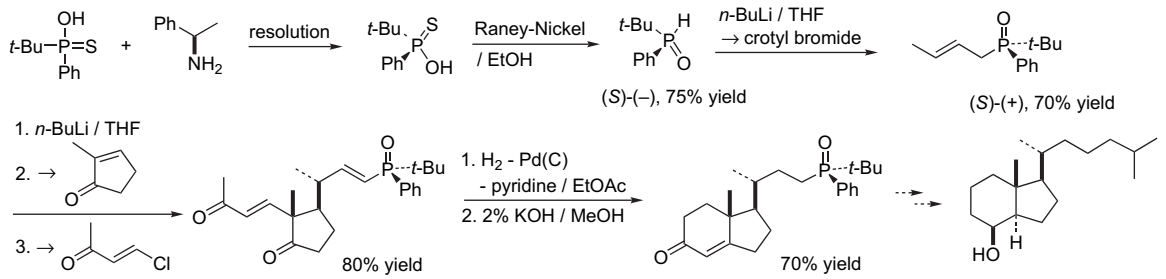
A few years earlier, Haynes and co-workers had proposed an interesting strategy for constructing the optically active CD-hydrindanol intermediate based on a tandem asymmetric conjugate addition of the homochiral lithiated (*E*)-butenylphosphine oxide to 2-methylcylopentenone followed by in situ enolate trapping with β-chlorovinyl ketone. The key feature of this transformation included a total control of the stereochemistry of the C(13), C(17) and C(20) centers accounted for by a 10-membered trans-fused chair–chair transition state of the intermediate enolate. The enantiomerically pure starting material was prepared by resolution of racemic phosphinothioic acid with (*S*)-(−)-α-methylbenzylamine, desulfurization with Raney nickel, and allylation of the resulting phosphine oxide. Subsequent intramolecular aldol condensation produced the hydrindenone and Windaus–Grundmann ketone should be obtained by transposition of oxygen from C(9) to C(8), elaboration of the trans-ring junction (see Daniewski's method in Scheme 51), and Wittig–Horner-mediated side chain extension. This sequence was successfully reported for the functionalization of the racemic CD-intermediate hydrindenone prepared with the use of (*E*)-but-2-enyldiphenylphosphine oxide (Scheme 34).[72]



Scheme 32.



Scheme 33.



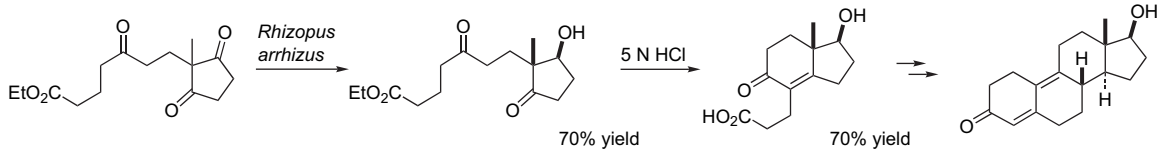
Scheme 34.

3. Desymmetrization of 2-substituted 1,3-cyclopentanediones

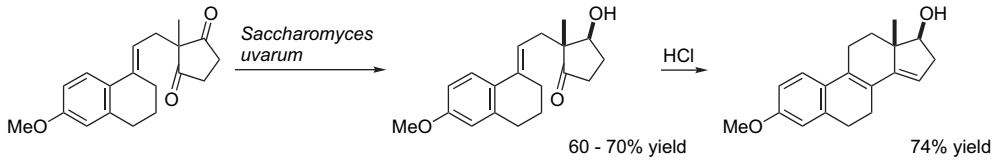
3.1. By a microbial approach

Resolution processes usually result in a loss of the undesired enantiomer. However, this problem can be circumvented by exploiting the prochiral character of some intermediates. As previously reported, Michael addition of 2-methylcyclopentane-1,3-dione to 5-oxo-6-heptenoic acid methyl ester and Torgov reaction from 6-methoxy-1-tetralone afforded the respective substituted achiral secodiones possessing a prochiral center. Subsequent acid-catalyzed aldol condensation with one of the ketone functions generates the bicyclic and tetracyclic structures. At this stage, a stereogenic center is created, suggesting that a preliminary differentiation of both carbonyl groups should give access to only one enantiomer. In 1966, French and German industries reported at the same time the enantioselective microbial reduction of the intermediate dione leading to the optically active secoketol. Roussel-Uclaf researchers proposed the use of *Rhizopus arrhizus* Fischer for the reduction of the cyclopentane-1,3-dione, represented in Scheme 35,[73] while those of Schering employed *Saccharomyces uvarum* with the Torgov secodione (Scheme 36).[74] Then, the latter was used as starting material in the synthesis of optically active 11-ketoestrane derivatives.[75]

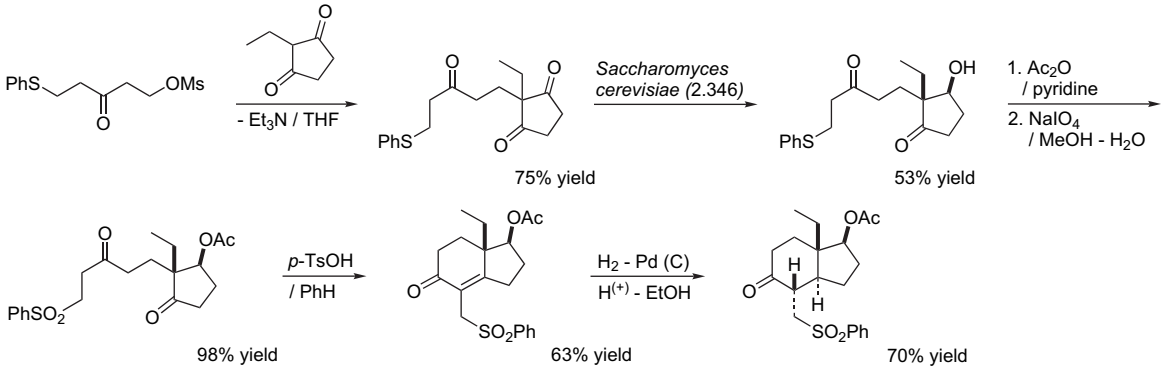
A particularly interesting optically active steroid CD-ring synthon was prepared by Dai and Zhou through a microbial asymmetric reduction of a prochiral trione, obtained by alkylation of 2-ethylcyclopentane-1,3-dione with 3-oxo-5-(phenylthio)-pentyl methanesulfonate, using *Saccharomyces cerevisiae*. After sulfur oxidation, the generated sulfone underwent an acid-catalyzed cyclization to an unsaturated ketosulfone, readily converted into *trans*-hydrindanone after selective catalytic hydrogenation of the enone motif (Scheme 37).[76]



Scheme 35.



Scheme 36.



Scheme 37.

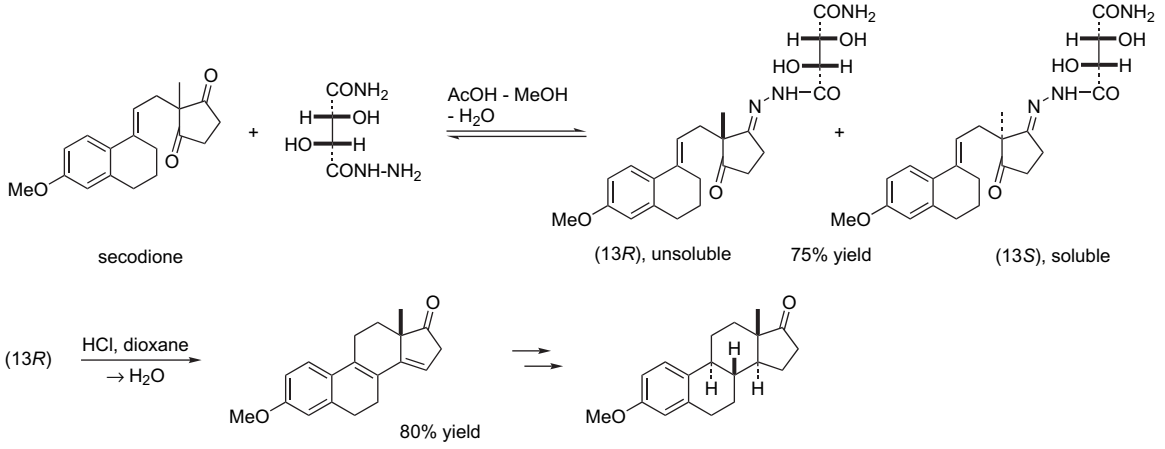
3.2. By formation of diastereoisomers

Roussel-Uclaf chemists have observed that L-tartramic acid hydrazide placed in aqueous methanol with traces of acetic acid could react reversibly with the Torgov secodione and only one of the diastereoisomers precipitated. Treated with HCl in dioxane, this compound cyclized into a (+)-estrone precursor (Scheme 38).[77]

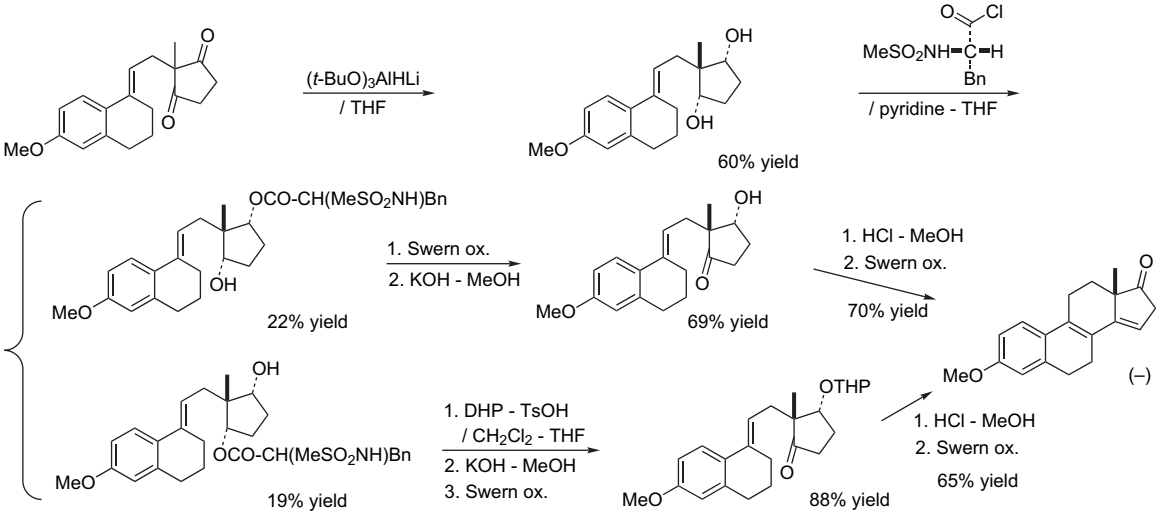
In another approach, Nara and co-workers reported the enantioconvergent synthesis of an optically pure steroid intermediate by considering first the stereoselective reduction of the Torgov secodione in *meso*-diol followed by its partial esterification with *N*-mesyl (*S*)-phenylalanyl chloride as a chiral reagent. The diastereoisomers were separated by chromatography and converted into a unique optically pure estrone precursor via a sequence of protection–deprotection–oxidation and a final acid-promoted cyclization (Scheme 39).[78]

3.3. By organometallic catalysis

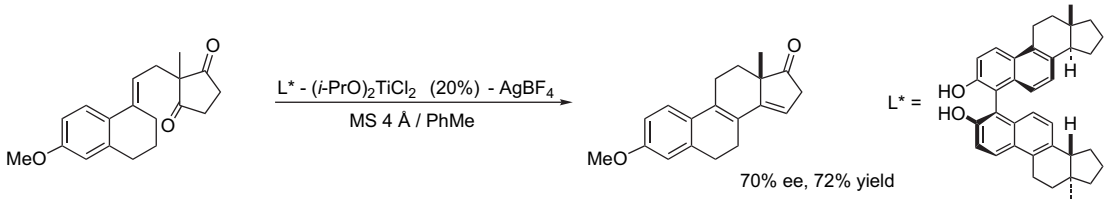
More recently, Enev and co-workers from Schering AG reported the first catalytic and enantioselective cyclization of the well-known methyl secodione required in the Torgov approach to estrone. This methodology involved an elegant asymmetric desymmetrization of the cyclopentanedione unit promoted by a new sterically demanding bis-steroidal titanium complex. In terms of yield and ee, this approach showed promising results, compared to the existing microbiological and chemical methods (Scheme 40).[79]



Scheme 38.



Scheme 39.



Scheme 40.

3.4. By asymmetric induction with amino acids

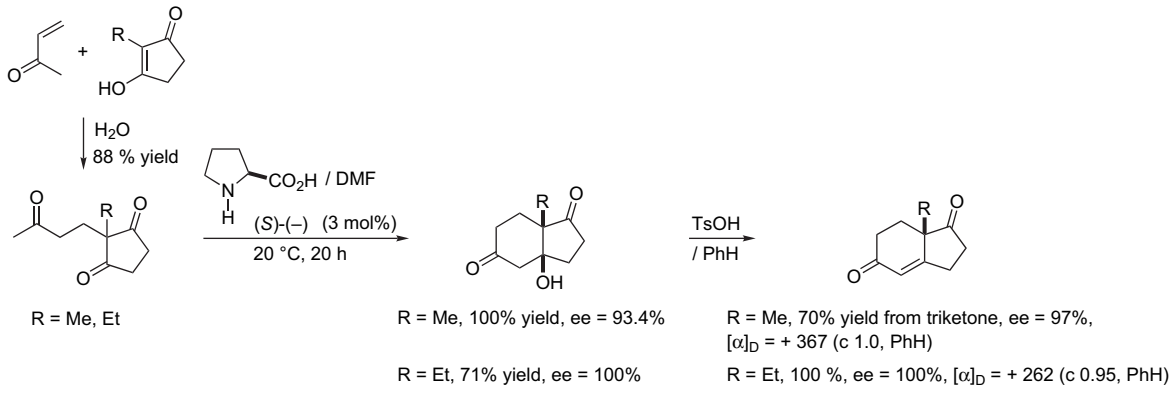
3.4.1. Hajos–Parrish–Eder–Sauer–Wiechert reaction. Michael addition of 2-substituted cyclopentane-1,3-diones to vinyl ketone reagents generates a prochiral triketone, the subsequent intramolecular aldol condensation of which forms the six-membered ring of the indenedione skeleton. In 1971, Hajos and Parrish[80] on the one hand and Eder, Sauer, and Wiechert on the other,[81] showed that upon exposure to amino acids in the natural L-configuration, in particular L-proline, prochiral triketones led to ketol or enedione adducts with excellent chemical yields and with close to 100% enantiomeric excess in some cases. This so-called Hajos–Parrish–Eder–Sauer–Wiechert reaction represents one of the most significant developments in the organic synthesis field.[82,83]

To perform this transformation, Hajos and Parrish operated with a catalytic amount of (*S*)-(−)-proline in anhydrous DMF at room temperature. Dehydration of the resulting *cis*-ketol under acidic conditions gave the (+)-indenedione. This synthesis was all the more interesting in that the triketone resulting from the addition of the 2-methylcyclopentane-1,3-dione to methyl vinyl ketone could be obtained with 88% yield by using water as solvent (Scheme 41).[84,85]

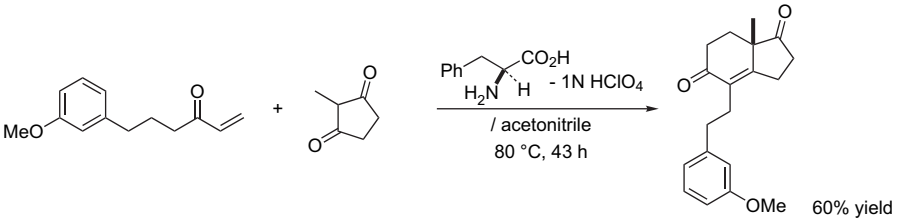
Eder, Sauer, and Wiechert used harsher experimental conditions to achieve the ring closure of the triketone leading directly to the indenedione. The reaction was carried out in acetonitrile containing 1 N perchloric acid and heated at 80 °C for 20 h. For the triketone resulting from the addition of methylcyclopentanedione to methyl vinyl ketone, the chemical yield reached 86% and the optical yield 84%. Other examples were reported showing that proline and phenylalanine were the catalysts of choice for this transformation and that (*S*)-amino acids induced the formation of indenediones with an *S* configuration (Scheme 42).

Several hypotheses were proposed to rationalize the enantioselectivity of this cyclization process.[82] First of all, it was indicated that the reaction is accompanied by a weak negative non-linear effect, suggesting that two molecules of proline are implied in the transition state.[86] Moreover, Agami observed that the enantiomeric excess strongly decreases when the proline concentration is reduced.[87] It was believed that the proline reacts with the methyl ketone moiety, generating the corresponding enamine, which adds to the most reactive *pro-R* ring carbonyl and the second molecule of proline acts according to a general base catalysis.[86,88] As depicted in Scheme 43, cyclization to (*R*)-indenedione is affected by the major steric repulsion between the acid function and the carbonyl group favoring the access to the *S* enantiomer. This mechanism was reinforced by Hanessian experiments showing that *cis*-4,5-methanoproline exhibits a catalytic ability similar to that of proline, whereas trans-4,5-methanoproline is less efficient (Scheme 44).[89] Finally, DFT theoretical calculations reported by Houk allowed the conclusion that the proline carboxylic acid was involved in an electrophilic activation of a cyclopentanedione carbonyl group.[90]

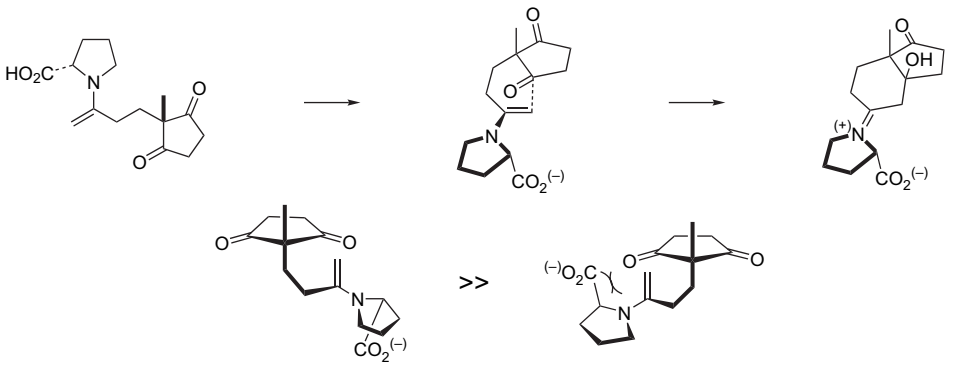
The Hajos–Parrish methodology was applied to the preparation of the Wieland–Miescher ketone, starting from methyl vinyl ketone and 2-methyl cyclohexane-1,3-dione. The required cyclohexenone was formed by aldol ring closure with an overall yield of 71% and a 70% optical yield (Scheme 45). A subsequent crystallization afforded the enantiomerically enriched naphthalenedione.[91–93] A few



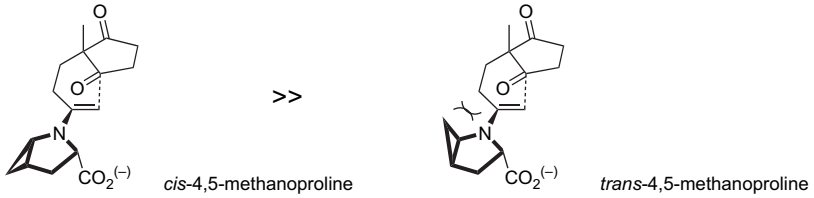
Scheme 41.



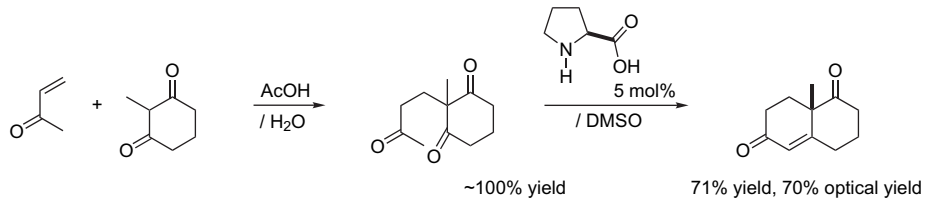
Scheme 42.



Scheme 43.



Scheme 44.



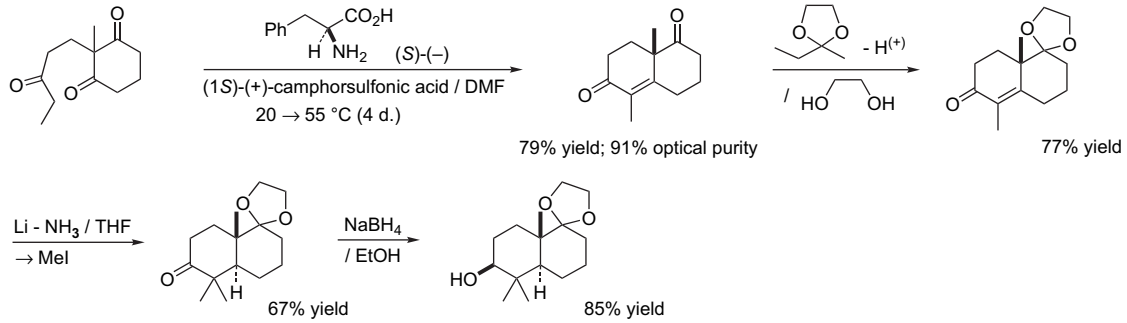
Scheme 45.

years later, Harada improved this procedure in order to obtain the bicyclic diketone in an optically pure form.[94]

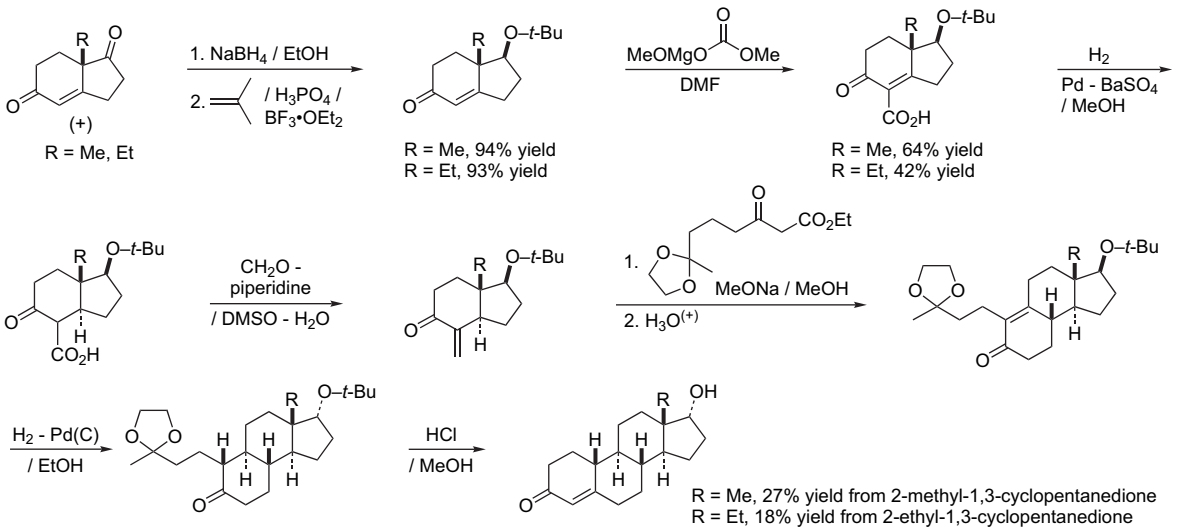
As part of their work on the preparation of a steroid biosynthesis inhibitor, Hagiwara and Uda studied the enantioselective cyclization of the triketone affording the methylated Wieland–Miescher ketone. After several tests, they found that the best method consisted of using phenylalanine in DMF in the presence of camphorsulfonic acid. In addition, they stressed that the control of the temperature must be increased slowly to reach a maximum of 55 °C. An enantiomeric excess of approximately 80–90% was obtained from either D- or L-amino acid (Scheme 46).[95]

3.4.2. Use of indenediones in steroid synthesis.

3.4.2.1. Syntheses of 19-nor-steroids. The previous (+)-indenedione was largely employed by chemists as a building block for the synthesis of various steroids. Hajos and Parrish started with an approach to 19-nor-steroids and showed, for the first time, that the asymmetric cyclization leading to the optically active bicyclic dione can be carried out on a 50–250 g scale. The subsequent unsaturated keto acid was isolated with a modest yield, but the starting indenedione could be recycled. The key step was the diastereoselective hydrogenation of the keto acid that gave rise to the unique *trans*-indanedione. Michael addition of a substituted β-keto ester to the methylene ketone followed



Scheme 46.



Scheme 47.

by aldol annulation, saponification, and decarboxylation furnished the tricyclic compound, which was converted into the required 19-nor-steroid (Scheme 47).[96]

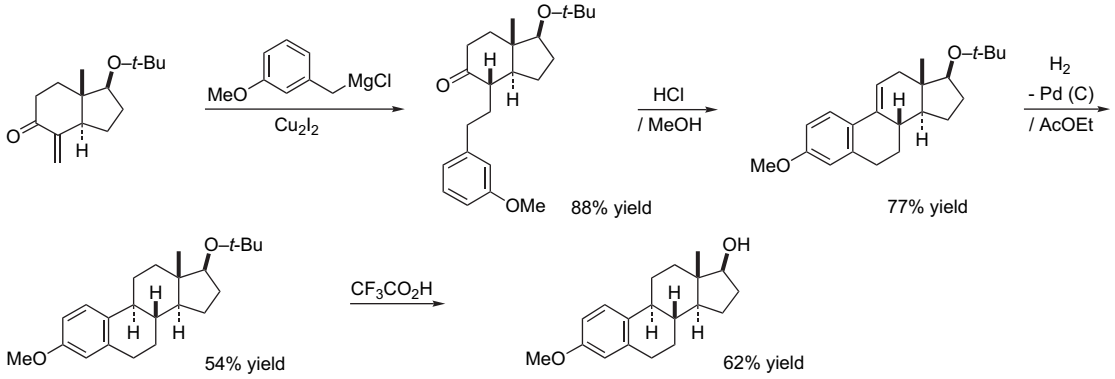
Hoffmann-La Roche chemists reported a straightforward route to (+)-estrone methyl ether based on a similar sequence using the chiral bicyclic α-methylene ketone intermediate. A conjugate addition of *m*-methoxybenzyl Grignard reagent produced the tricyclic ketone and an acid-catalyzed aromatic substitution completed the synthesis. The 18-ethyl steroid analog was prepared according to a similar approach (Scheme 48).[97]

The optically active β-keto ester, prepared by methylation of the previous keto acid, was successfully exploited by Tsuji and co-workers as a key intermediate in the synthesis of (+)-19-nor-testosterone. A suitable enone reagent was easily prepared via a palladium-catalyzed dimerization of butadiene and was subjected to a Michael addition with the bicyclic keto ester derivative. A sequence of annulation and stereocontrolled hydrogenation reactions afforded the target tetracyclic compound (Scheme 49).[98]

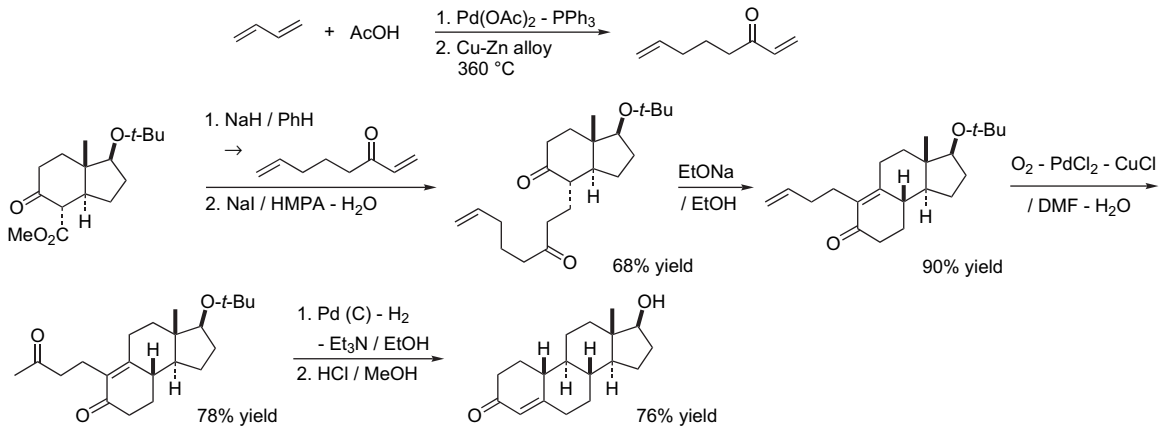
The conjugated enolate of the *tert*-butyl protected ketol coming from the Hajos–Parrish (+)-indenedione could be alkylated at the C(8)-position by suitable alkyl chains in order to build up A- and B-rings of steroid backbones. Thus, Eder trapped the transient enolate with *m*-methoxyphenacyl bromide to prepare estradiol,[99,100] whereas the addition of 2-bromo-3′,5′-dimethoxypropiophenone led to (+)-1,3-dimethoxy-7β-methyl-1,3,5(10)-estratrien-17-one.[101] Both trans BC- and CD-ring junctions were established during the diastereoselective hydrogenation of their respective indenofuran intermediates. Construction of the B-ring by acid-assisted cyclization and further transformations furnished estradiol in a stereoselective manner (Scheme 50).

In 1988, Daniewski reported a convenient access to a *trans*-hydrindanedione from the indenedione CD-building block involving a reductive addition of a *tert*-butylcopper/DIBALH complex. Condensation of the formed diisobutylaluminum enolate with *m*-methoxyphenylacetaldehyde gave a 9,10-seco compound, which served as a precursor for the synthesis of estrone and 7-hydroxy-estrone, as presented in Scheme 51.[102]

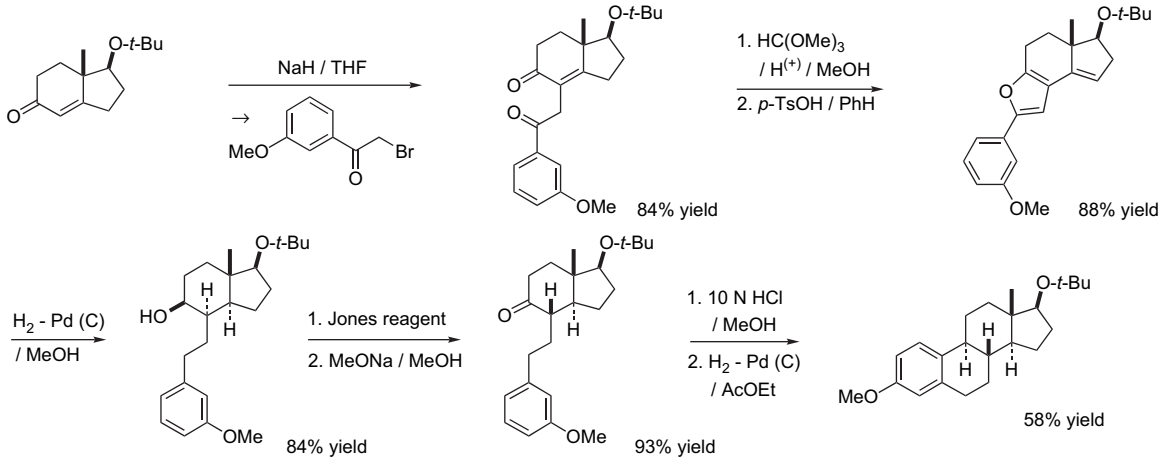
Sauer showed that formaldehyde in the presence of benzenesulfinic acid allowed the sulfonylmethylation of indenedione or its related keto ether. A significant result indicated that the α,β-unsaturated enone system could be hydrogenated selectively, giving the indanone with a trans-ring junction (Scheme 52). The α-sulfonyl carbanion was alkylated by



Scheme 48.



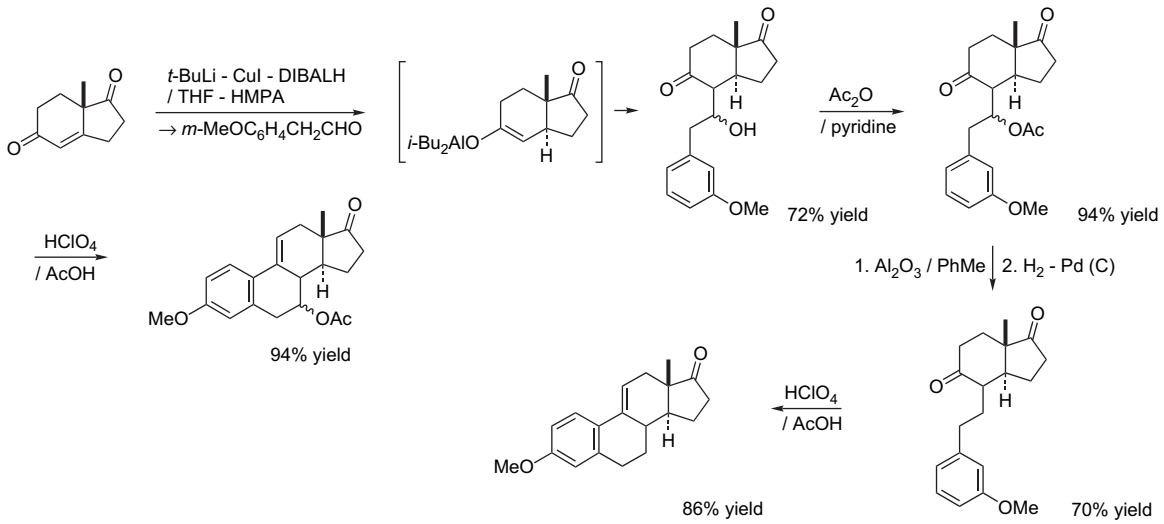
Scheme 49.



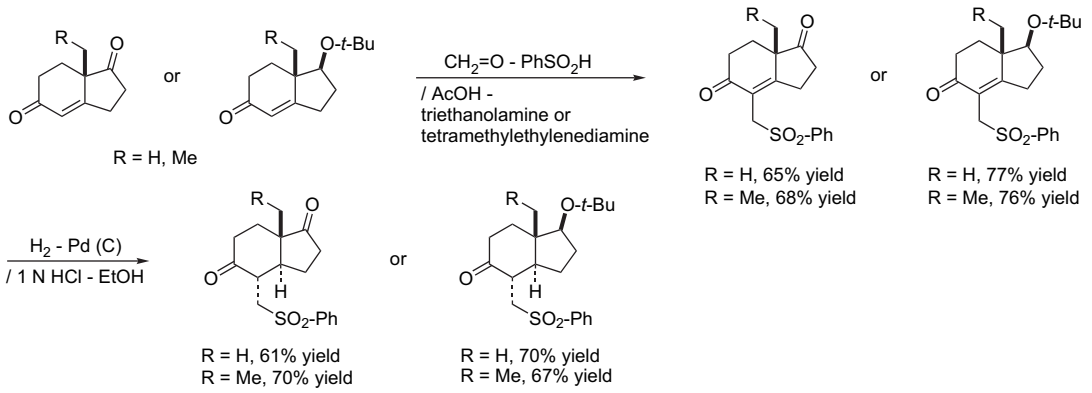
Scheme 50.

3,5-dimethoxybenzyl bromide in moderate yield. After separation, each epimer underwent acid-catalyzed cyclization. A better yield was obtained from the (*S*)-sulfone cyclization, and the tetracyclic adduct was then diastereoselectively reduced and derivatized to estrone analogs (Scheme 53).[103]

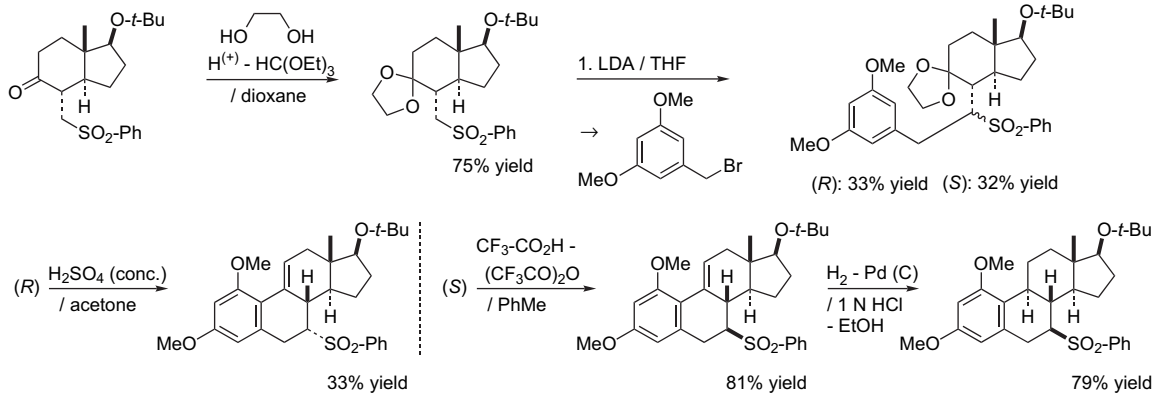
Alternatively, Sauer's *trans*-hydrindanone could be efficiently alkylated by a β-keto ester according to a sulfone elimination–Michael addition sequence. Several 19-nor-steroids were synthesized in good yields, and particularly des-A,19-di-nor-steroids (Scheme 54),[104,105] but the major



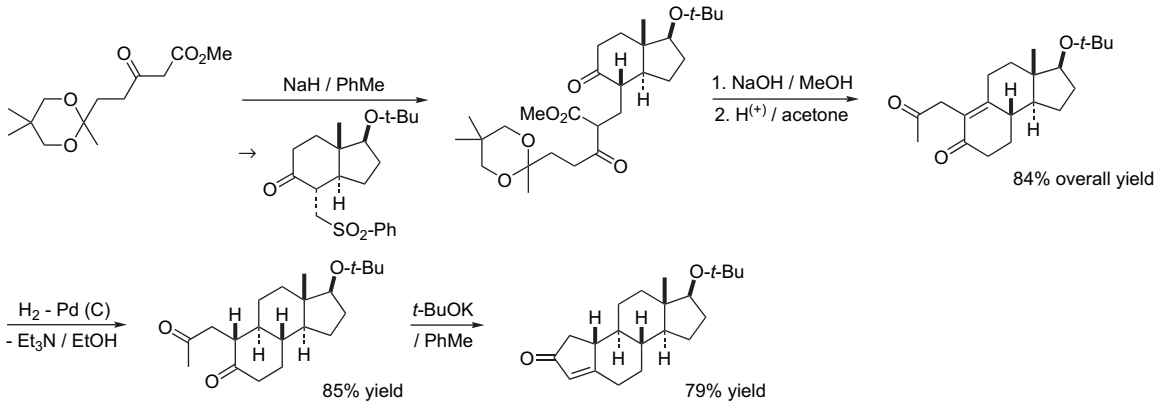
Scheme 51.



Scheme 52.



Scheme 53.

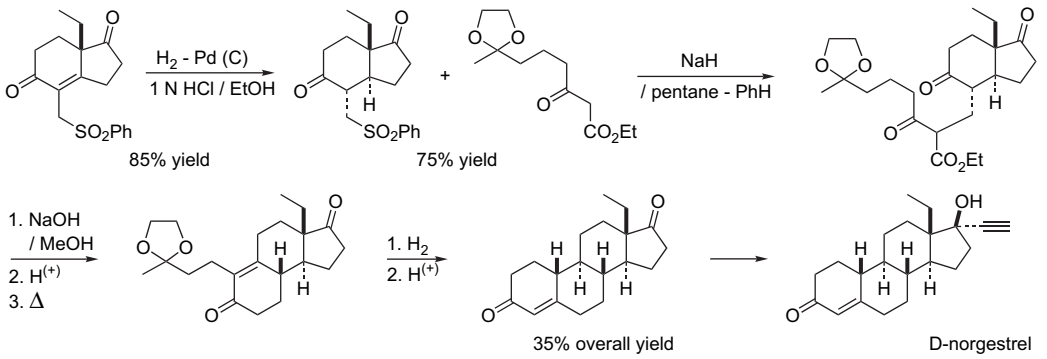


Scheme 54.

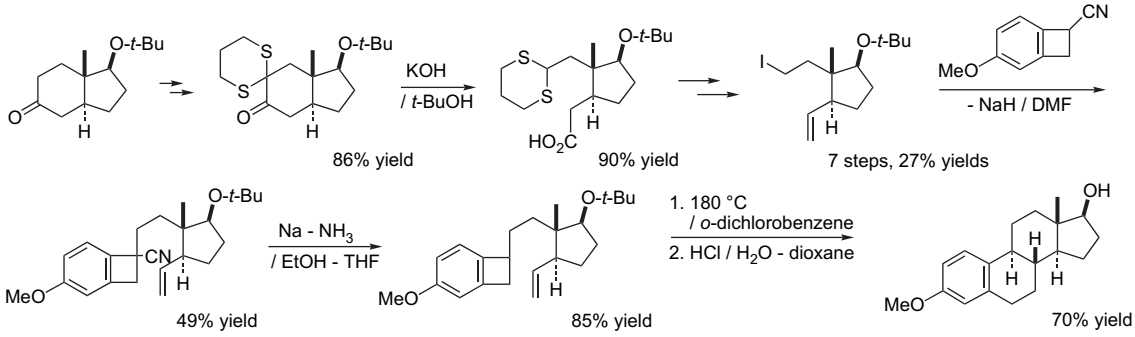
application of this alkylation process was reported in 1975 with the synthesis of the extraordinarily powerful progestational and ovulation inhibiting D-norgestrel steroid. The optically active 18-methyl-19-nor-androstenedione was prepared starting from the (+)-indenedione with a 35% overall yield and its ethynylation led to D-norgestrel (Scheme 55).[106]

In 1978, Kametani proposed a novel asymmetric approach to estradiol by an intramolecular cycloaddition reaction of a benzocyclobutene derivative involving an *o*-quinodimethane intermediate. The construction of the precursor proceeded via C-ring cleavage of the Hajos–Parrish indanone, derivatization to the primary alkyl iodide, and condensation with 1-cyano-4-methoxybenzocyclobutene at the C(11)-position. Although the yields are generally moderate to good, this convergent synthesis is long, particularly the access to the optically pure cyclopentane derivative, which requires 10 steps from the indanone (Scheme 56).[30a,107]

Daniewski suggested another route to a similar vinylcyclopentanone chiral synthon, easily accessible in nine steps from the Hajos–Parrish hydroxydione with a 28% overall yield. The sequence proposed was based on a regioselective



Scheme 55.



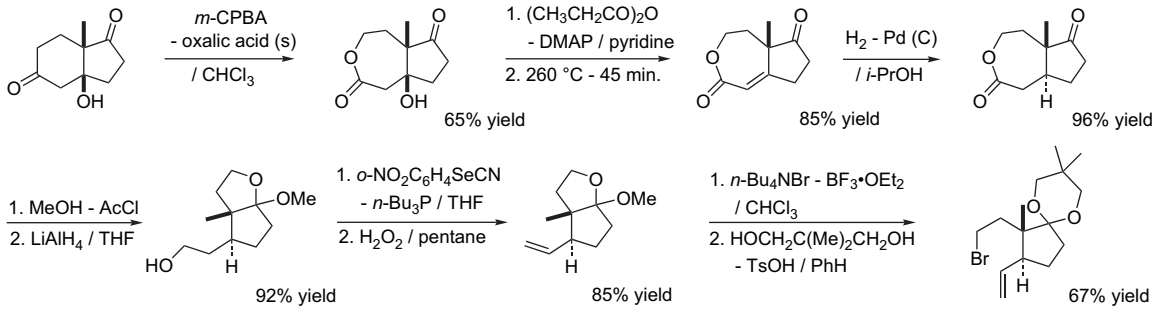
Scheme 56.

Baeyer–Villiger lactone formation and a stereospecific catalytic hydrogenation of the unsaturated bicyclic lactone intermediate. Further functional-group manipulations completed the synthesis of this building block (Scheme 57).[108]

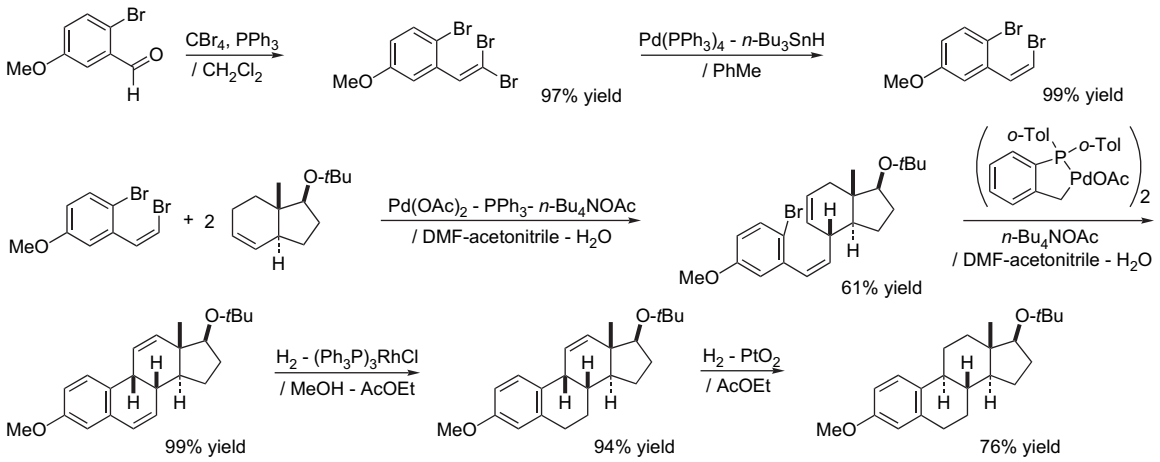
An original strategy was developed by Tietze and coworkers, who created the typical tetracyclic ring system of estrone using two consecutive pallado-catalyzed Heck reactions of a brominated bromovinylarene with an enantiopure hydrindene derived from the Hajos–Wiechert ketone. The high degree of stereoselectivity observed at the cross-coupling stage may be imposed by a shielding of the upper face of the alkene by the angular methyl, whereas the regioselectivity was totally unexpected and difficult to understand. Thus, intramolecular Heck reaction of the seco-B intermediate employing the Herrmann–Beller palladacycle gave the unusual cis-junction between C/D-rings and completed the steroidal skeleton. Hydrogenation of the cis-*anti*-trans compound with accompanying isomerization of the benzylic stereogenic center allowed the selective formation of the known estradiol derivative, which could be converted into estrone (Scheme 58).[109]

This methodology was applied to the synthesis of a novel 19-nor-steroid,[110] the D-homoestradiol analog,[111] aza-heterocyclic compounds,[112] and then the enantiopure thiasteroid obtained from the related dibromothiophene derivative (Scheme 59).[113] In a similar manner, the B-nor-estradiol could be prepared by a sequential chemoselective Suzuki-type reaction of an optically active 6-5 bicyclic boronic ester with 2-bromobenzyl chloride followed by intramolecular Heck coupling (Scheme 60).[114]

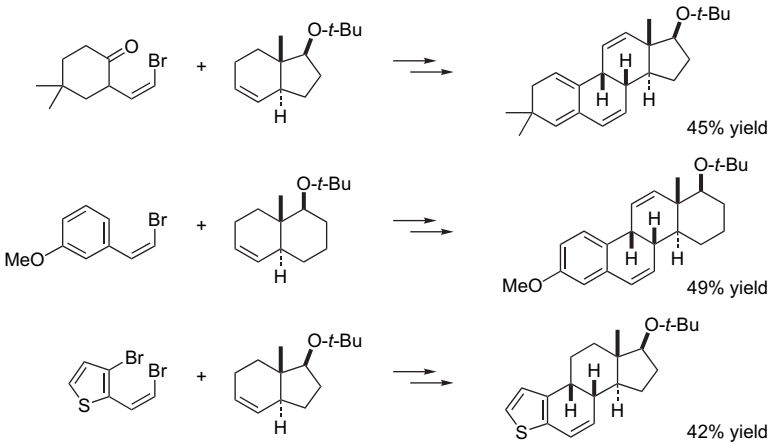
On the other hand, de Meijere and Sünnemann employed a combination of selective Stille–Heck cross-coupling reactions with optically pure *trans*-hexahydroindenylstannanes, 4-substituted 2-bromocyclohexenol triflates, and alkyl acrylates to give 1,6-disubstituted 1,3,5-hexatriene



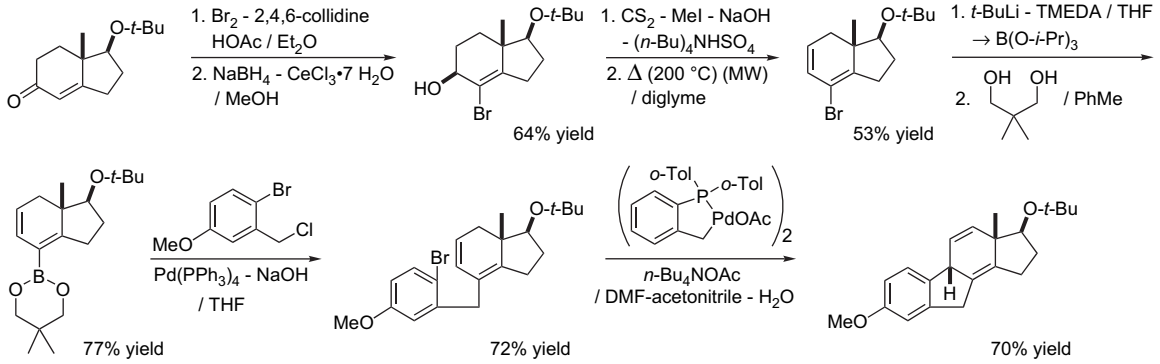
Scheme 57.



Scheme 58.



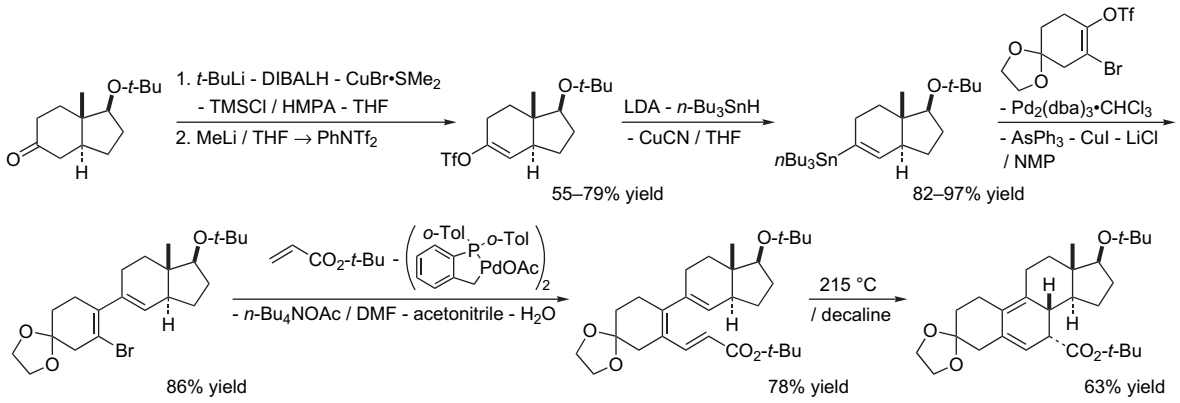
Scheme 59.



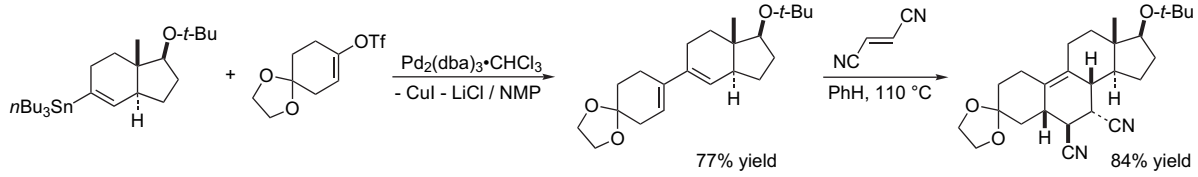
Scheme 60.

intermediates. To access the tetracyclic steroid skeleton, the seco-B trienic system was heated in decalin at 215 °C and underwent a 6π-electrocyclization with a high degree of outward disrotational selectivity leading to the unique trans-*anti* diastereoisomer (Scheme 61).[115] Alternatively, construction of the B-ring can also be realized utilizing a sequence of Stille cross-coupling and Diels–Alder cyclization reactions with a range of dienophiles. Novel steroid analogs possessing a C-5β configuration were obtained (Scheme 62).[116]

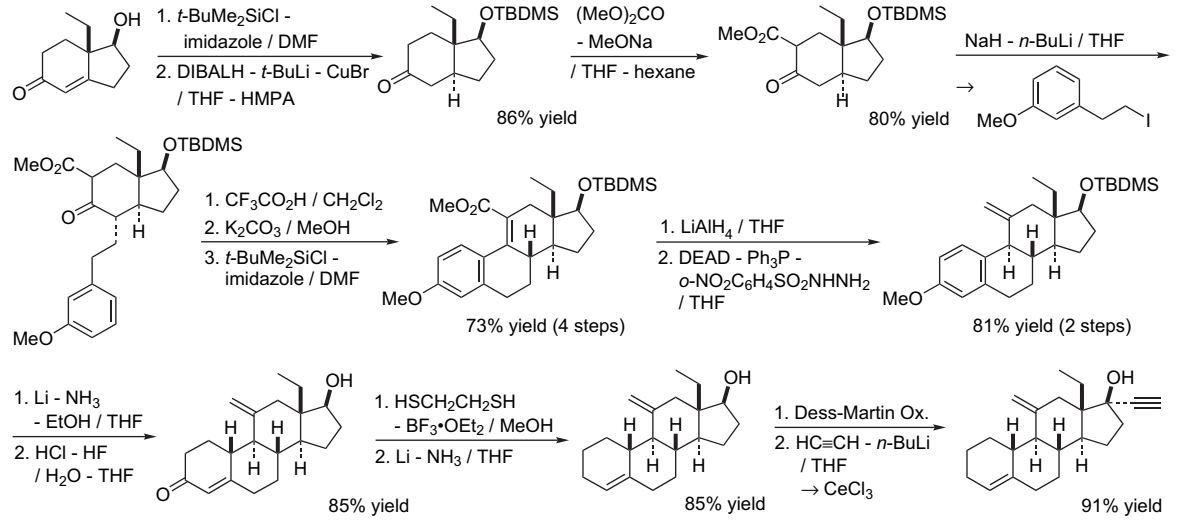
Corey and Huang used the readily available enantiopure indenolone resulting from a Robinson annulation with ethylcyclopentanedione to prepare the third-generation oral contraceptive, desogestrel. A clean cationic cyclization favored the construction of the tetracyclic framework and the correct B/C trans-junction was established during the formation of the critical 11-*exo*-methylene group. The synthesis is short, very efficient, and potentially useful for industrial production (Scheme 63).[117]



Scheme 61.



Scheme 62.



Scheme 63.

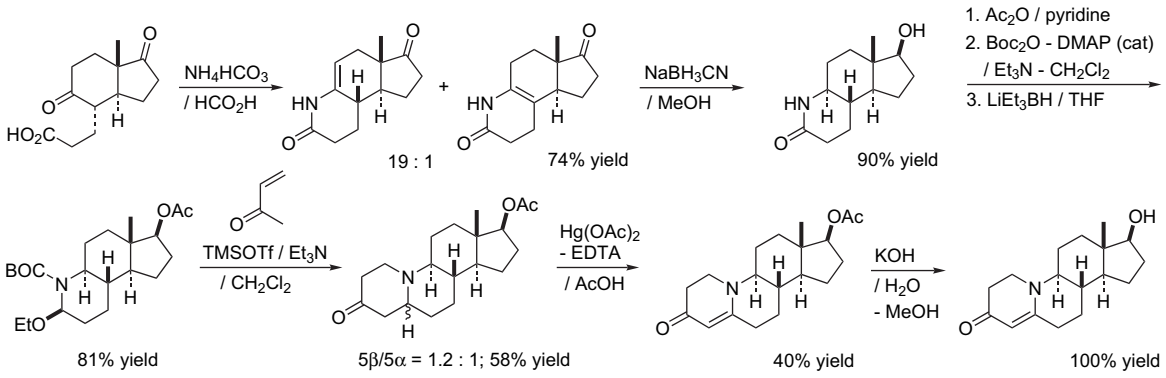
From the acid obtained either from (+)-indenedione or from the microbial degradation of sterols present in soya beans and marketed by Pharmacia & Upjohn,[118] Guarna and coworkers synthesized 19-nor-10-azasteroids, a new class of substrates that inhibit the enzyme, steroid 5α-reductase. A key cyclization step, based on a tandem *N*-(acyloxy)iminium ion–Michael addition reaction, constructed the A-ring and provided the azasteroidal compounds (Scheme 64).[119]

3.4.2.2. Syntheses of testosterone. *ent*-Steroids could be prepared by considering the Hajos–Parrish (−)-indenedione obtained with the available (*R*)-proline. Firmenich chemists[19] were interested in the synthesis of *ent*-testosterone involving two Wichterle annulations for the construction of the B- and A-rings, respectively, as depicted in Scheme 65.[88a,120]

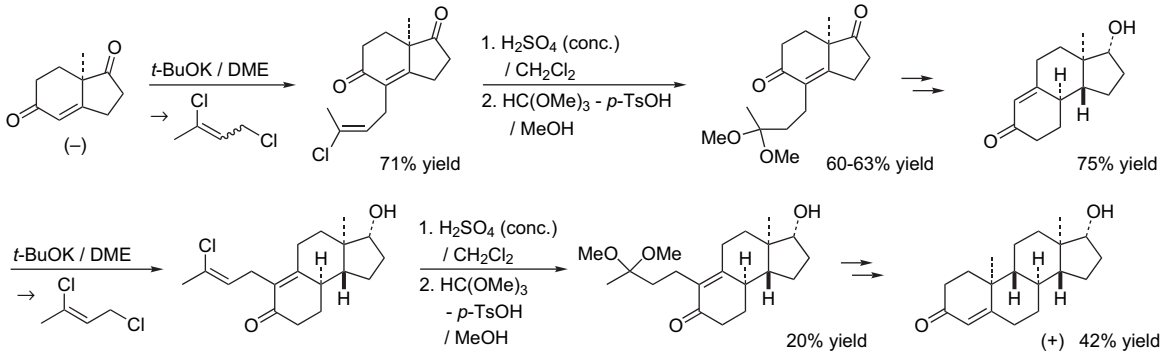
Taking for inspiration the work of Hajos and Parrish, Rychnovsky prepared *ent*-testosterone from (−)-indenedione and also used it to synthesize *ent*-cholesterol (Scheme 66).[121]

After having reported in 1985 a long synthesis of androsterone implying an intramolecular Diels–Alder reaction for the construction of the steroidal A/B-ring system (Scheme 67),[122] Fukumoto proposed in 1990 a new synthetic methodology consisting of a 1,3-dipolar cycloaddition of a nitrile oxide used to build the B-ring and facilitate the elaboration of the cyclohexenone A-ring (Scheme 68).[123]

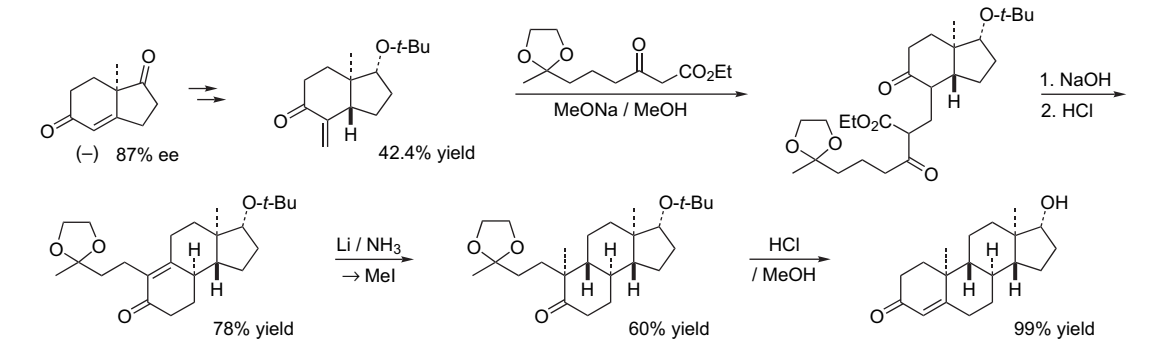
3.4.2.3. Syntheses of cholesterol. From (−)-testosterone (or *ent*-testosterone), Kumar and Covey realized the introduction of the cholesterol side chain via a Me_2AlCl-mediated ene reaction of (*Z*)-*exo* cyclic olefin with 4-methyl-1-pentanal.



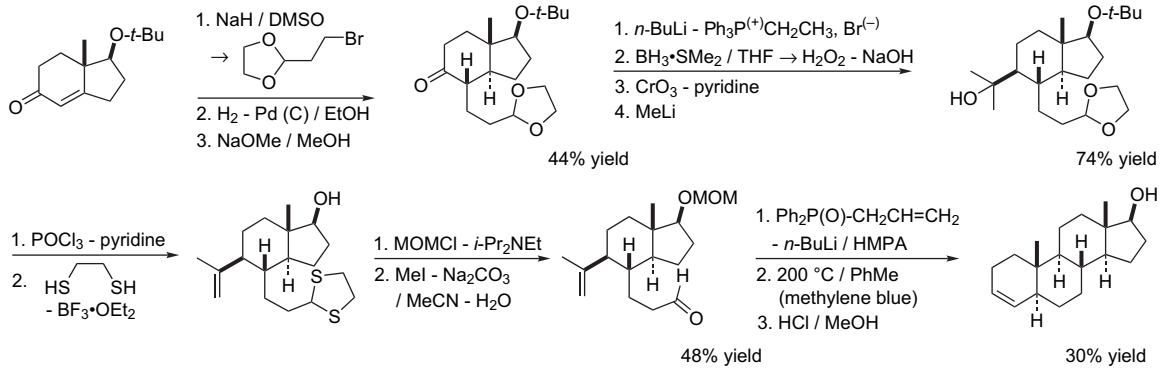
Scheme 64.



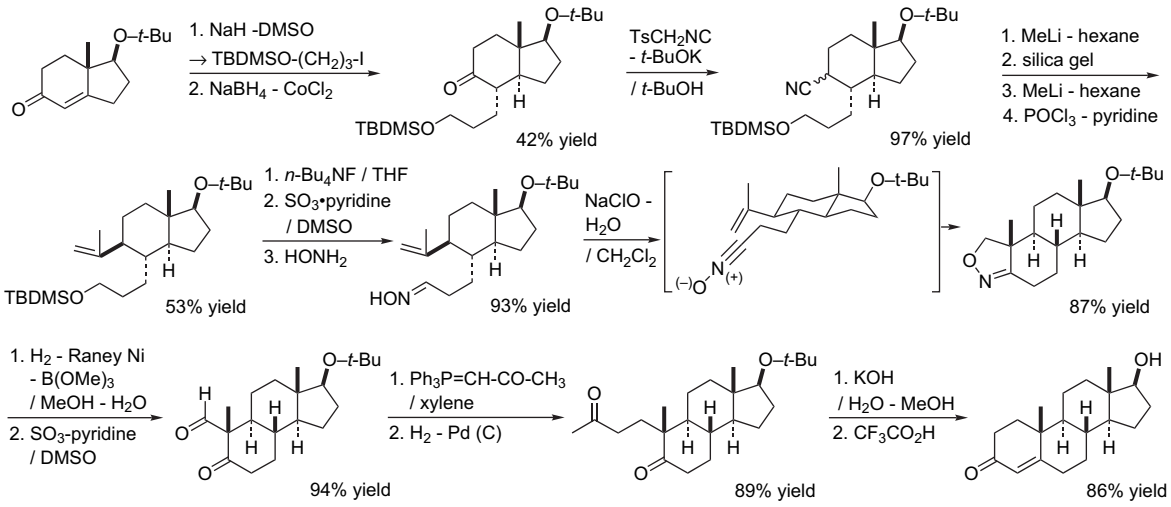
Scheme 65.



Scheme 66.



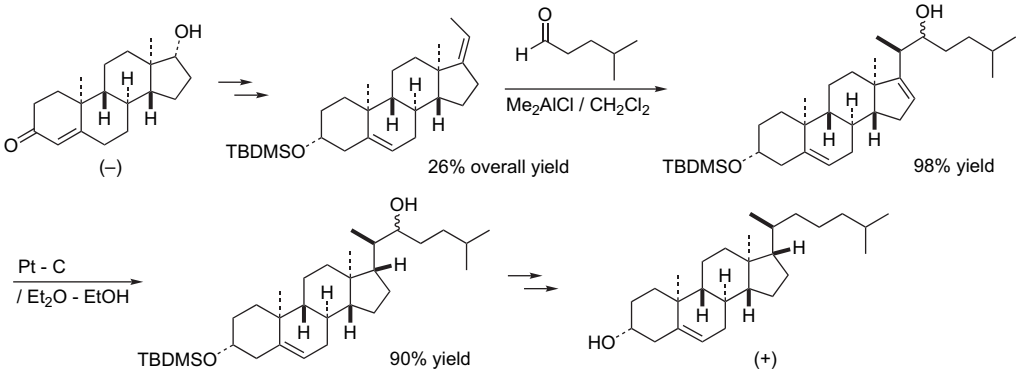
Scheme 67.



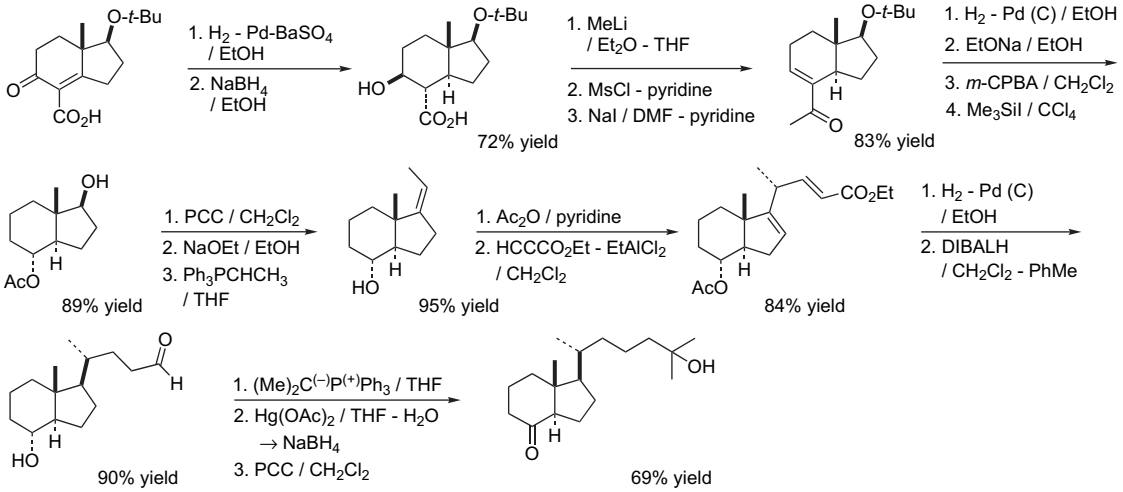
Scheme 68.

Selective hydrogenation of the resulting Δ^{16} double bond and removal of the 22-hydroxyl group gave the *ent*-cholesterol (dextrorotatory) with a 9.7% overall yield (Scheme 69).[124]

3.4.2.4. Syntheses of vitamin D derivatives. *(i) Construction of trans-fused CD-bicyclic systems by hydrogenation of C(8)-substituted indenones*: Baggiolini and co-workers from Hoffmann-La Roche exploited the keto acid, asymmetrically synthesized by Hajos and Parrish, to prepare the Windaus–Grundmann ketone hydroxylated at the C(25)-position. Catalytic hydrogenation of the unsaturated system established the C/D trans-ring junction and the 25-hydroxy side chain with the proper absolute configuration at C(20) was introduced by an ene reaction. This synthon was widely used in the synthesis of 1α-hydroxyvitamin D metabolites such as 1α,25-dihydroxycholecalciferol (Scheme 70).[125]



Scheme 69.



Scheme 70.

Then, the same authors elaborated the CD-bicyclic portion of 1α,25(*S*),26-trihydroxycholecalciferol. The remote chiral center at C(25) was introduced through a regionspecific and diastereoselective 1,3-dipolar cycloaddition of the C(23) nitrone with methyl methacrylate. After separation from the other three components, the desired (23*S*,25*S*)-isomer was isolated in 71% yield. The starting nitrone was prepared from the Inhoffen–Lythgoe diol by one-carbon homologation and the resulting isoxazolidine converted into the triol CD-ring synthon. Condensation of the hydrindanone with the phosphinoxy anion, the synthesis of which is described in Section 6.2, completed the synthetic approach to 1α,25(*S*),26-trihydroxycholecalciferol (Scheme 71).[126]

In 1986, Fukumoto reported a new stereocontrolled approach to the Windaus–Grundmann ketone and vitamin D_3 involving the asymmetric synthesis of des-AB-cholestane and 8α-(phenylsulfonyl)-des-AB-cholestane from the optically pure (−)-indenedione. The reaction sequence proposed by Fukumoto and reported in Scheme 72 is long, but relatively efficient.[127]

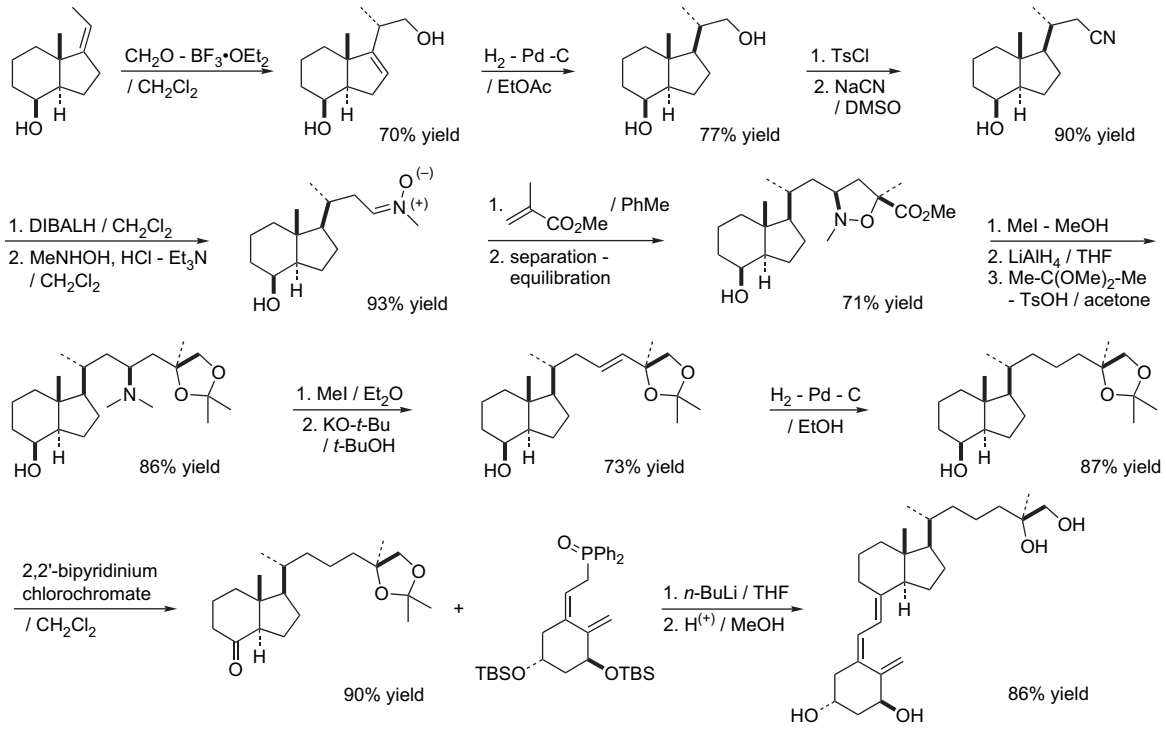
As reported by Mouriño, the Hajos–Parrish indenedione could be converted into the vitamin D *trans*-hydrindanol fragment by using a key hydroxyl-directed hydrogenation of the advanced hydrindenol intermediate in the presence of Wilkinson's catalyst (Scheme 73).[128] This building block provided access to a *trans*-ethenyl-hydrindene, which represents a potent steroid CD-ring diene precursor (Scheme 74).[129]

In a synthesis of estradiol developed by Rigby, the *trans*-ethenyl-hydrindene participated in a [6π+4π] cycloaddition process with a substituted thiepin dioxide chromium(0) complex and the resulting cycloadduct underwent a Ramberg–Bäcklund rearrangement that liberated the tetracyclic steroid nucleus. Routine functional-group changes afforded the steroid target (Scheme 75).[130]

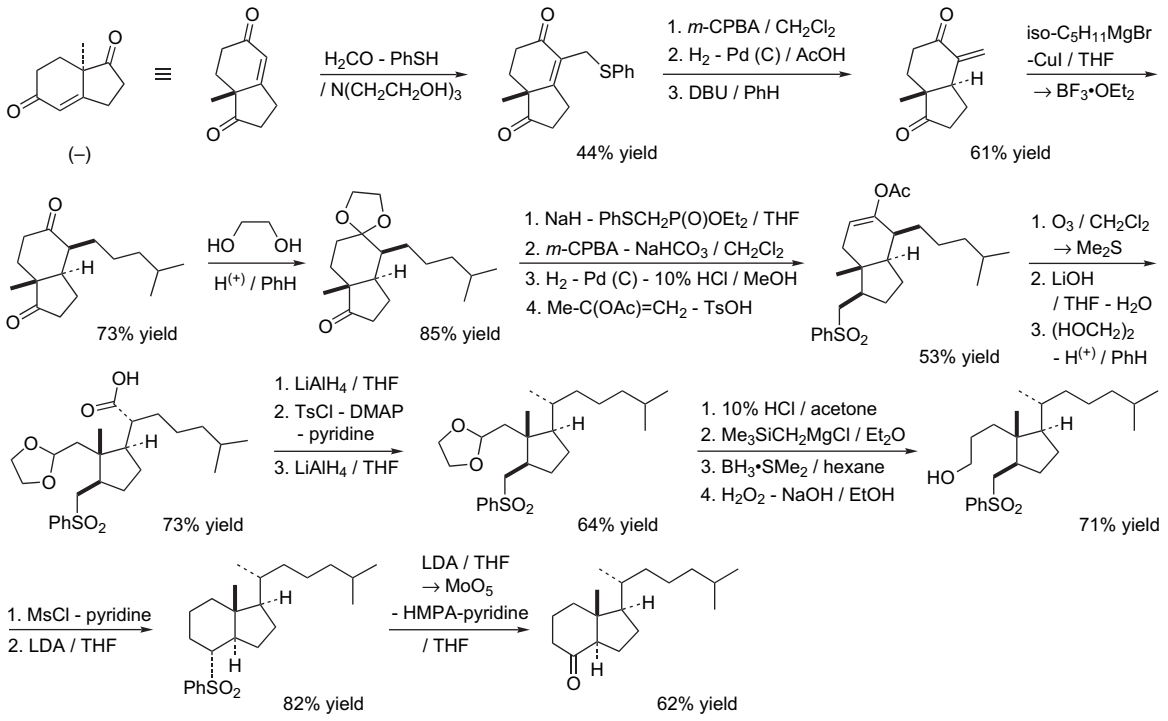
Tietze and Subba Rao proposed an alternative method for reducing the indenone to the trans-fused bicyclic system featuring an efficient palladium-catalyzed hydrogenolysis of an allylic formate (Scheme 76).[131]

(ii) Construction of cis-fused CD-bicyclic systems by selective hydroboration–oxidation sequence: the 14,20-bis-*epi*-Inhoffen–Lythgoe diol derived from (+)-indenedione or obtained by degradation of vitamin D_2 was used by Vandewalle to prepare 14,20-bis-*epi* analogs of 1α,25-dihydroxy-19-nor-vitamin D_3. From an advanced indene intermediate, construction of the *cis*-fused hydrindane with an 8-hydroxy function was realized by selective hydroboration–oxidation of the β-face, and the introduction of the methyl group at the C(20)-position with the unnatural (*R*)-configuration was performed either by diastereoselective enolate methylation according to the work of Wicha and co-workers (Scheme 77)[132] or by reductive alkylation of the unsaturated ester (Scheme 78).[133]

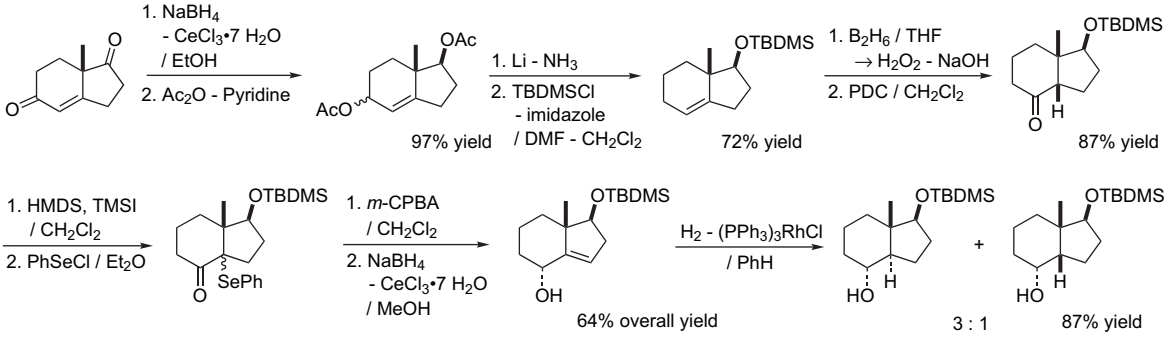
(iii) Construction of trans-fused CD-bicyclic systems by reductive epoxide ring opening: Daniewski proposed another strategy to obtain *trans*-hydrindanes based on a simpler six-step synthesis starting from the well-known enedione and comprising a copper/DIBALH-induced generation of the diisobutylaluminum enolate and its bromination, reduction of the resulting α-bromoketone to bromohydrin, and base-catalyzed epoxide formation followed by



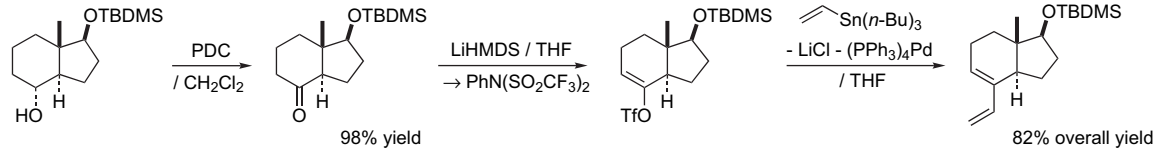
Scheme 71.



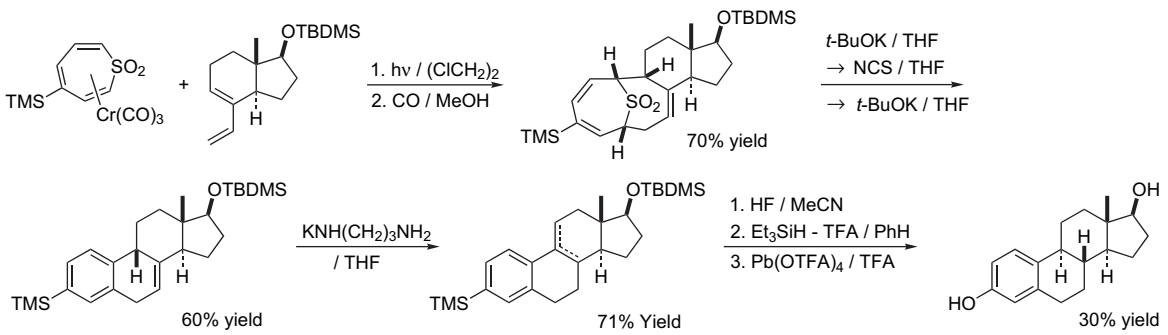
Scheme 72.



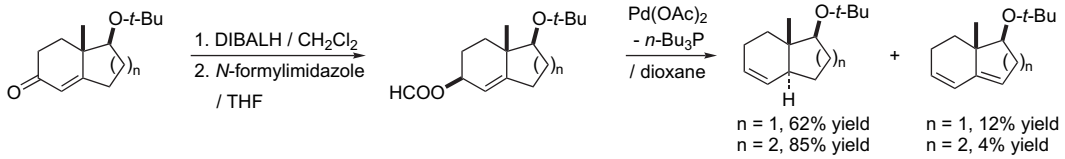
Scheme 73.



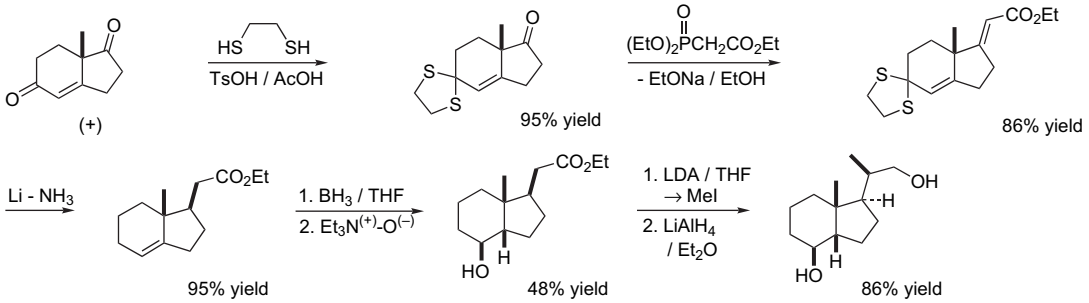
Scheme 74.



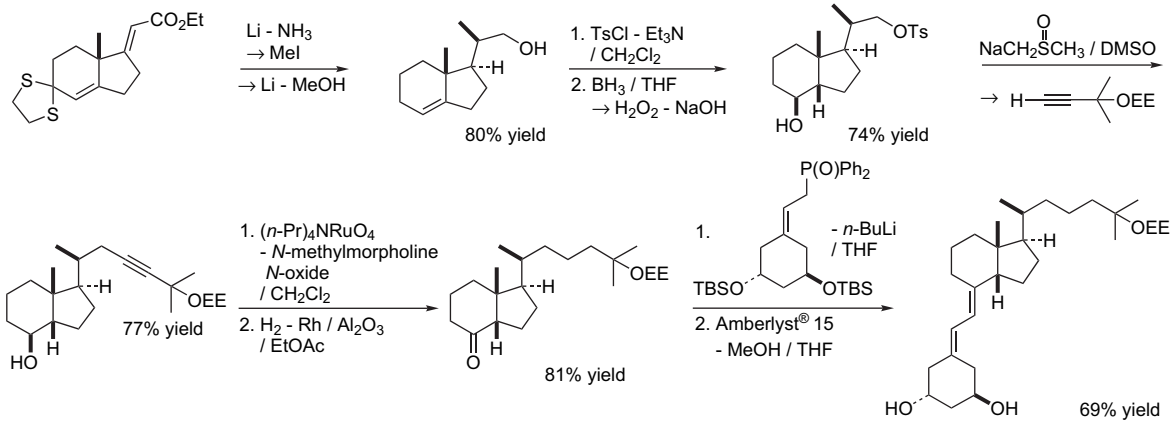
Scheme 75.



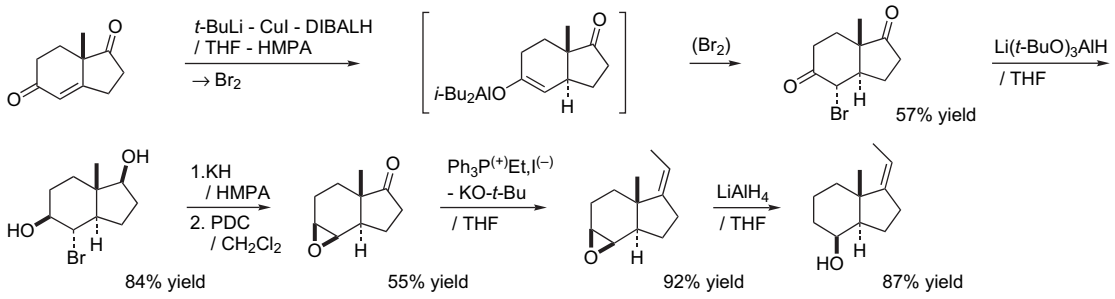
Scheme 76.



Scheme 77.



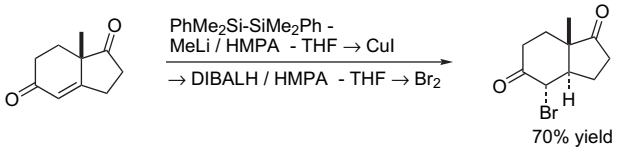
Scheme 78.



Scheme 79.

regioselective LAH ring opening. Multiplication of the given yields resulted in a 21% overall yield (Scheme 79).[134]

The reductive bromination step of the Hajos dione was then improved by the use of a novel silylcopper catalyst, dimethylphenylsilylcopper(I), more efficient than *tert*-butylcopper(I), which increased the overall yield to 26% (Scheme 80).[135]



Scheme 80.

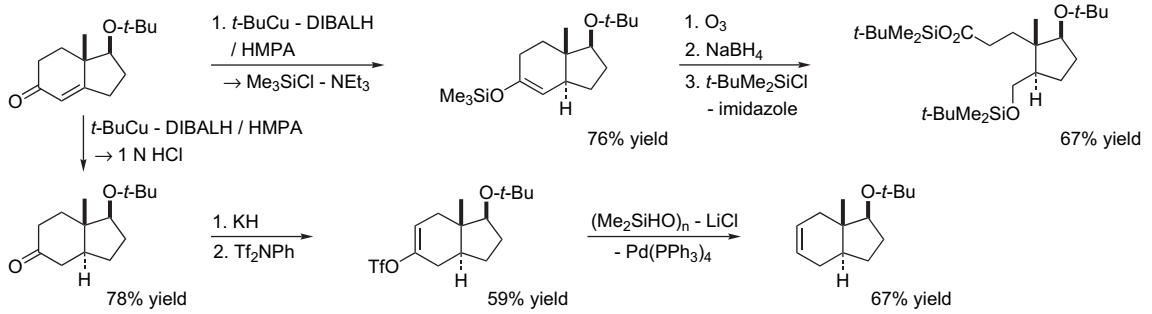
Several intermediates for the synthesis of steroids including enantiomerically pure indene derivatives and 1,2,2,3-tetra-substituted cyclopentanes have been synthesized, starting from the *trans*-hydrindane product of 1,4-reduction (*t*-BuCu/DIBALH) of the Hajos–Parrish ketone (Scheme 81).[136]

Very recently, Wicha proposed two different approaches to the *trans*-hydrindane alcohol from a common *trans*-hydrindanediol for calcitriol synthesis. The key step was the reduction of the epoxide alcohol, prepared from the Hajos–Parrish dione by epoxidation of the allylic alcohol, at the quaternary carbon by the Hutchins procedure[137] ($NaBH_3CN$–$BF_3\cdot Et_2O$) (Scheme 82).[138]

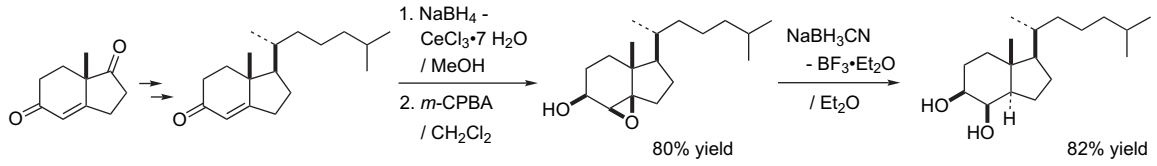
The vicinal diol product was regioselectively desoxygenated at the C(9)-position by two independent reaction routes. The first method was based on the elaboration of the C(8) monoacetate precursor of a thiocarbonate, which was reduced by tin hydride using the Barton–McCombie reaction (Scheme 83), whereas the second procedure consisted of a cyclic thiocarbonate formation, a subsequent regioselective opening of the thionocarbonate ring with methyl iodide and then lithium aluminum hydride reduction of the iodohydrin derivative (Scheme 84).[138b]

3.4.2.5. Miscellaneous syntheses. In a synthesis of 4,9(11)-androstadiene-3,17-dione reported by Schering and Hoffmann-La Roche, an alkylation of the optically active *tert*-butoxy- and methyl-substituted tetrahydroindanone with 1-chloro-7,7-*o*-phenylenedioxy-octane-3-one generated the corresponding diketone. This latter ketone was converted into the desA-steroid via a diene enol ether formation, as previously described. Methylation of the tricyclic enone gave predominantly the 10β-methyl compound, which was readily transformed into the title dione (Scheme 85).[139]

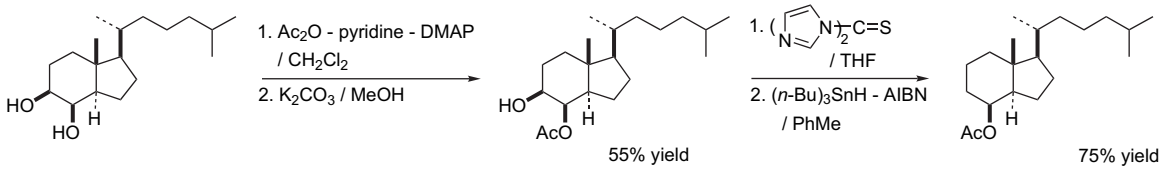
Overman and co-workers have achieved the construction of the tetracyclic core of complex cardenolides such as (−)-ouabain. In their strategy, an optically active cyclopentane D-ring ester, readily available from (+)-Hajos–Parrish indenedione, was linked to an enantiopure A-ring fragment



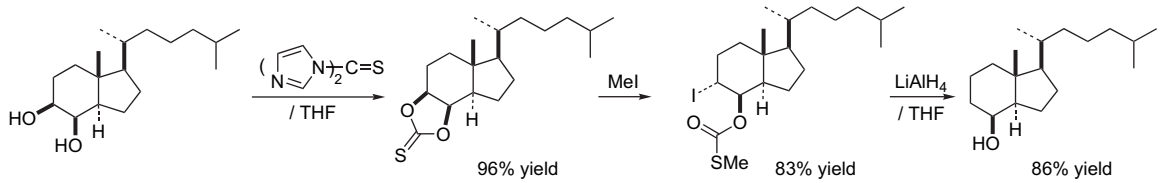
Scheme 81.



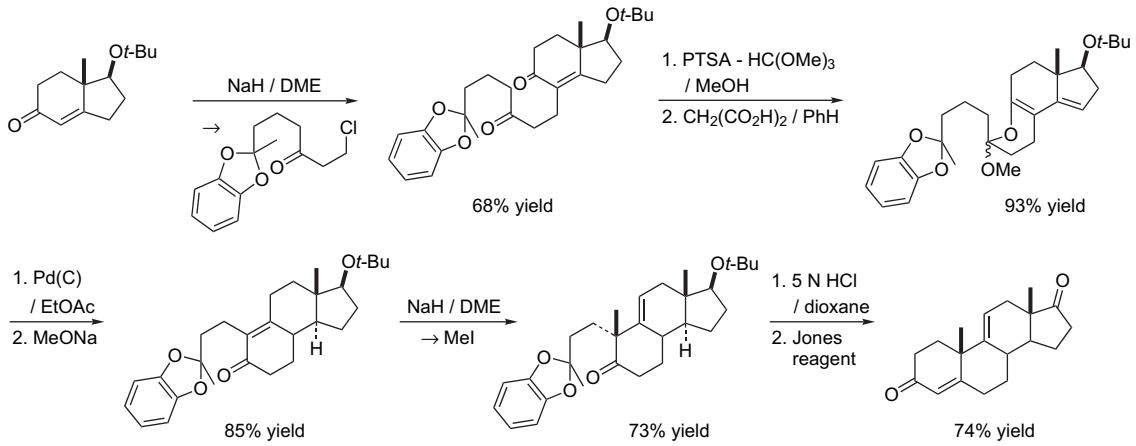
Scheme 82.



Scheme 83.



Scheme 84.



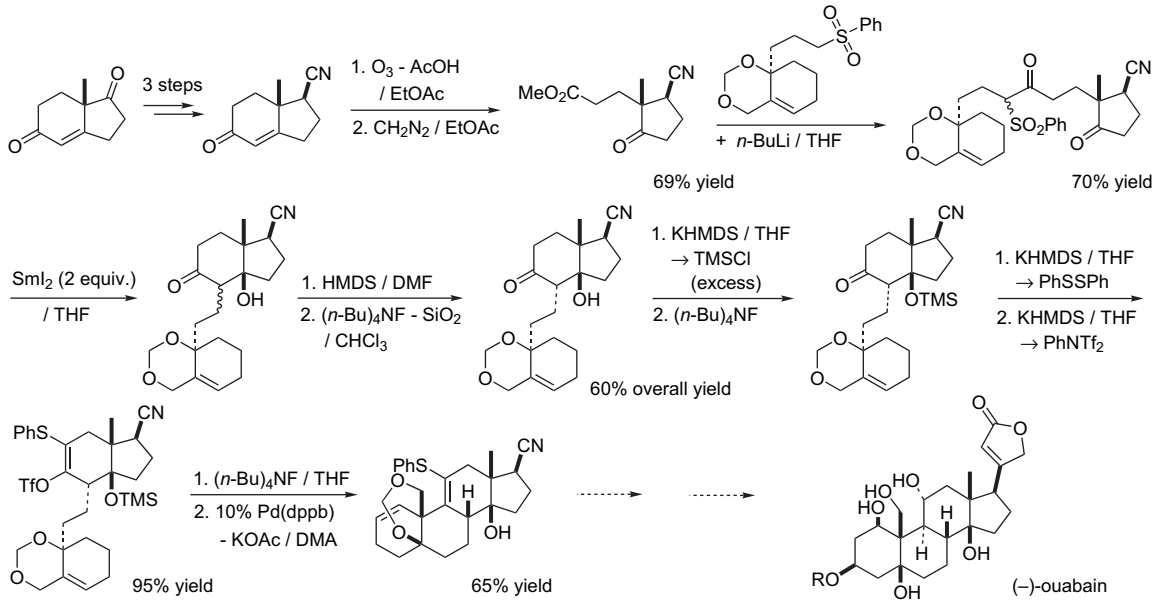
Scheme 85.

via the addition of its α-lithiated sulfone moiety. Subsequent reductive enolization and aldol cyclization led to the hydrindanone and an intramolecular Heck coupling reaction between an α-sulfenyl enol triflate and a trisubstituted alkene served as pivotal steps to form the steroid skeleton (Scheme 86).[140]

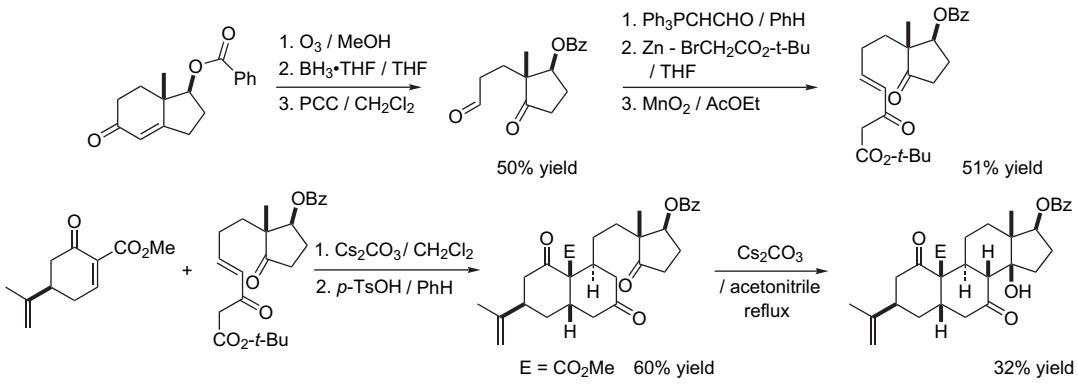
In order to obtain 14β-hydroxy steroids, Deslongchamps and co-workers prepared substituted Nazarov reagents, starting from a known chiral bicyclic enone, as described in Schemes 87 and 88.[141] These were then condensed with derivatives of (−)-carvone via first an anionic cycloaddition of the corresponding enolates followed by a decarboxylation and a base-catalyzed aldol reaction of the resulting triketones. The same methodology was applied to the convergent synthesis of other new interesting steroidal backbones (Scheme 89).[142]

3.4.3. Use of Wieland–Miescher ketone. Van Gool and Vandewalle examined an alternative approach to hydroxy *trans*-hydrindanones from (+)-Wieland–Miescher ketone and based on a D-ring contraction of the trans-fused decalone intermediate. In contrast to 13-methylated hydrindane systems, trans-fused decalins are more stable than the cis isomers that facilitate their access. Indeed, base-catalyzed equilibration of *cis*-decalone, obtained by hydroboration and oxidation, can afford the thermodynamically more stable *trans*-decalone. Cleavage of the α-hydroxyketone and Dieckmann cyclization generated the target molecule as a precursor of the Inhoffen–Lythgoe-type diol used in the synthesis of vitamin D metabolites and analogs (Scheme 90).[143] A synthesis of new vitamin D_3 analogs with a decalin-type CD-ring fragment, prepared starting from the (*S*)-Wieland–Miescher ketone, has been described, as outlined in Scheme 91.[144]

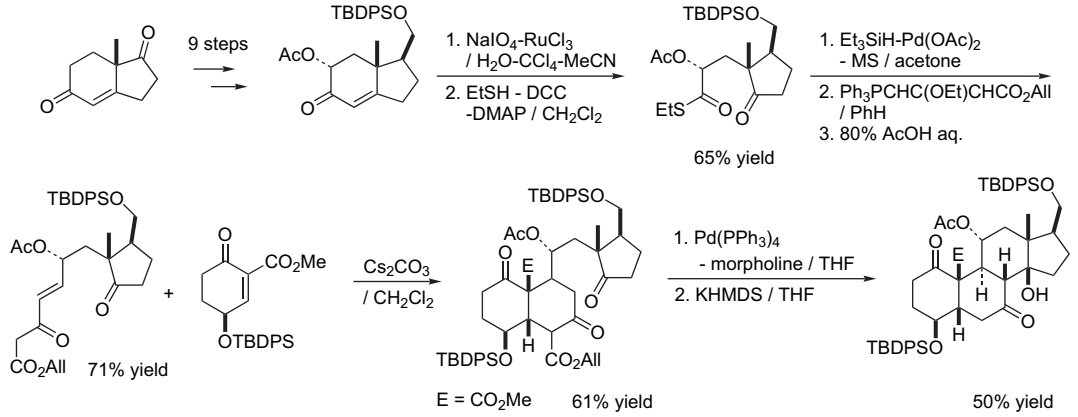
The Torgov-like reaction of 2-methylcyclopentane-1,3-dione with the allyl bromide derived from the enantiomerically enriched Wieland–Miescher ketone afforded the (+)-8,14-seco-4,9(11)-androstadiene-3,14,17-trione, which cyclized to 13ξ-androsta-4,8,14-trien-3,17-dione as a mixture of diastereomers. Only a slight induction of chirality from the



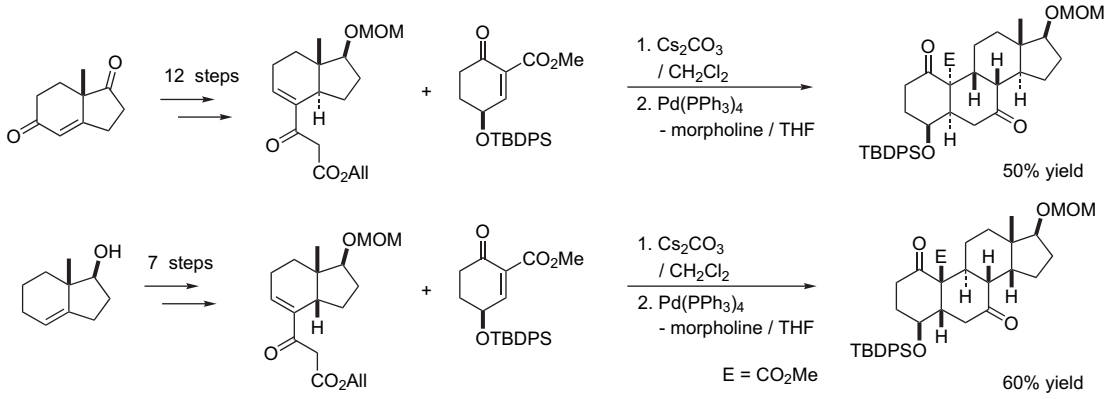
Scheme 86.



Scheme 87.



Scheme 88.

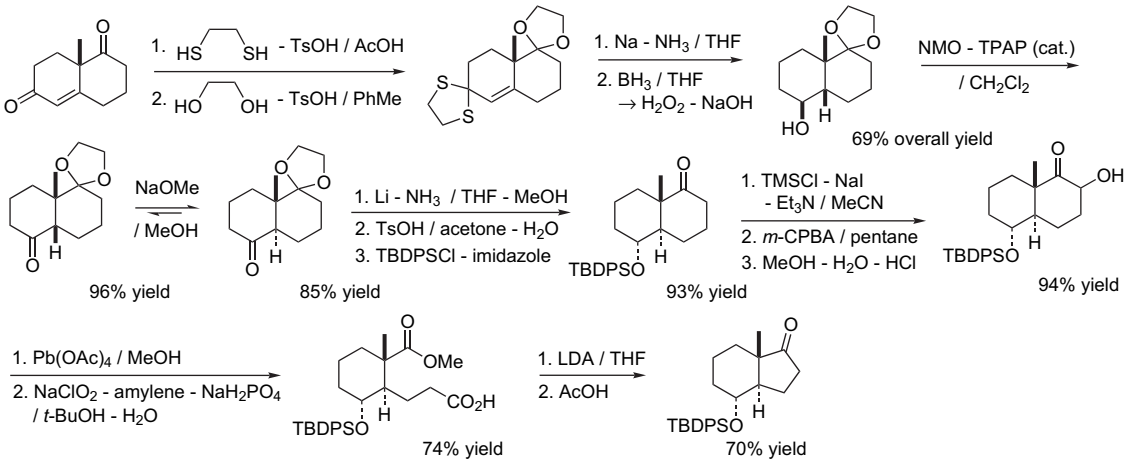


Scheme 89.

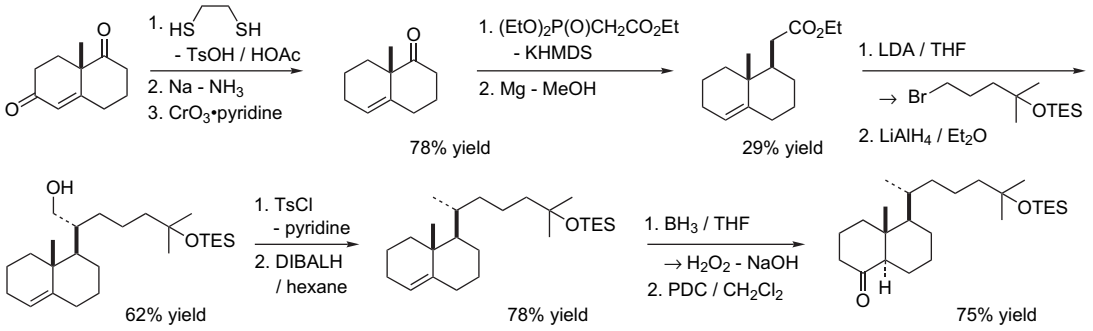
chiral center at C(10) to the newly formed center at carbon C(13) was detected (Scheme 92).[145]

The Wieland–Miescher ketone has also been used by Kametani and co-workers as a versatile building block for the stereoselective synthesis of (+)-5α-dihydropregnenolone. Their approach was first based on the formation of a tetracyclic intermediate, in which the B- and C-rings of the steroidal system were generated in one step from the optically active 1-ethenyl-2-[2-(4-methoxybenzocyclobutenyl)-ethyl]-1-methylcyclohexan-4-ol by an intramolecular cycloaddition reaction. The trans-fused hydrindane including the D-cycle of the steroid is generated by a series of laborious reactions (Scheme 93).[146]

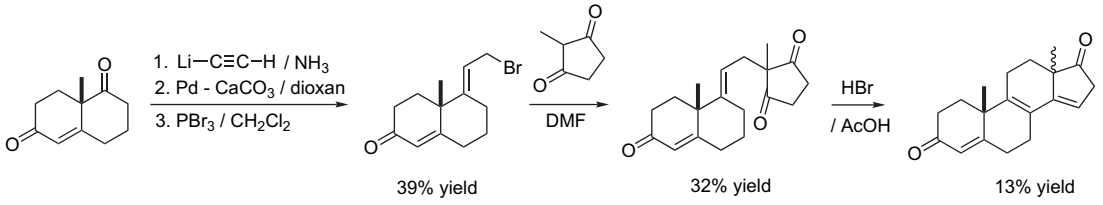
For the first time, Kametani and co-workers reported the synthesis of (+)-chenodeoxycholic acid, one of the two primary bile acids employed in the treatment of gallstones. The key optically active [2-(benzocyclobutenyl)ethyl]cyclohexane was prepared from the Wieland–Miescher ketone and the *cis*,*anti*,*trans*-fused D aromatic steroid backbone was generated during the intramolecular *o*-quinodimethane



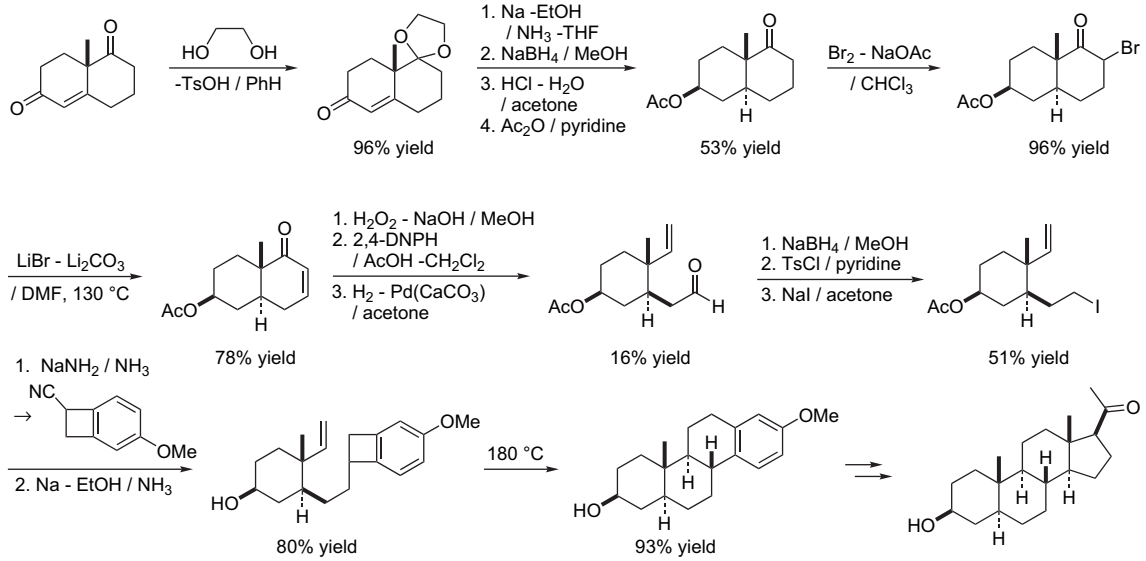
Scheme 90.



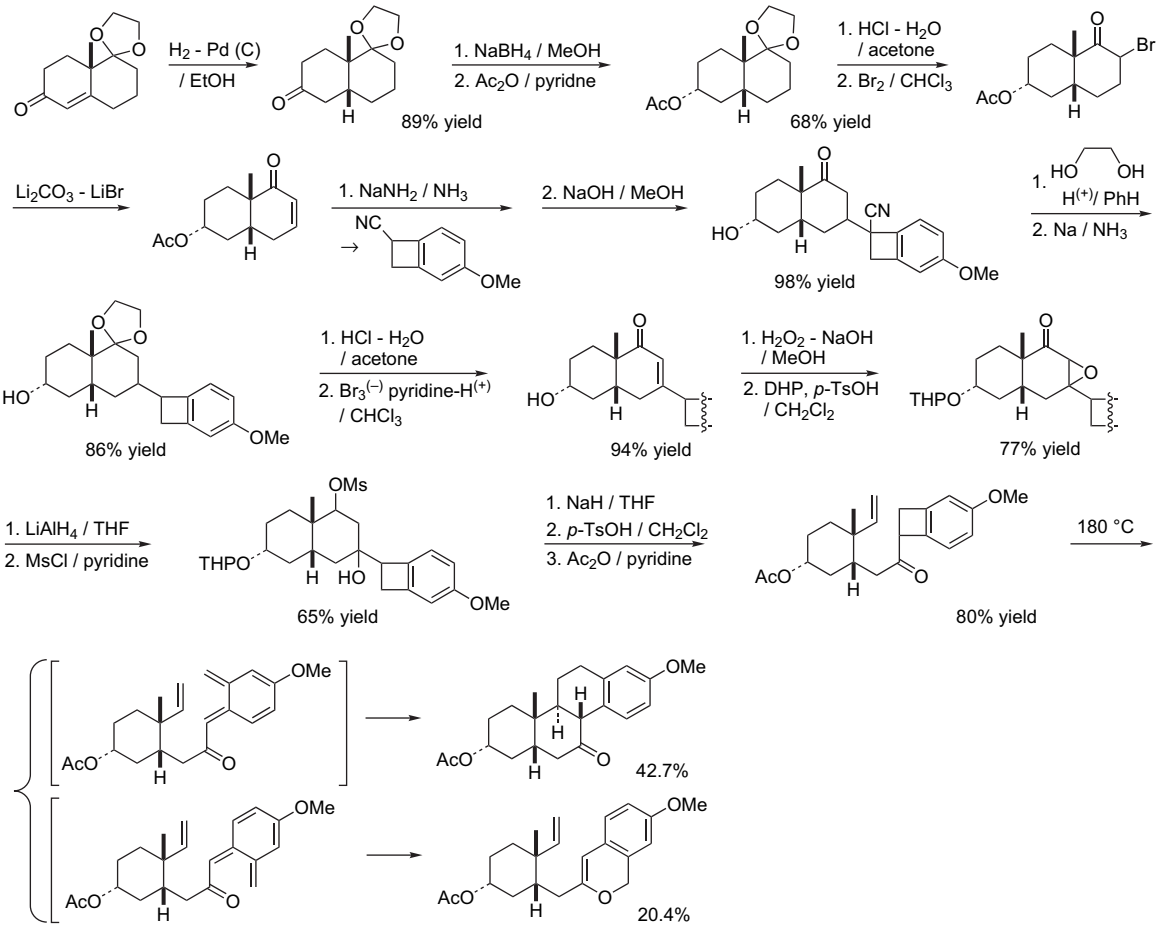
Scheme 91.



Scheme 92.



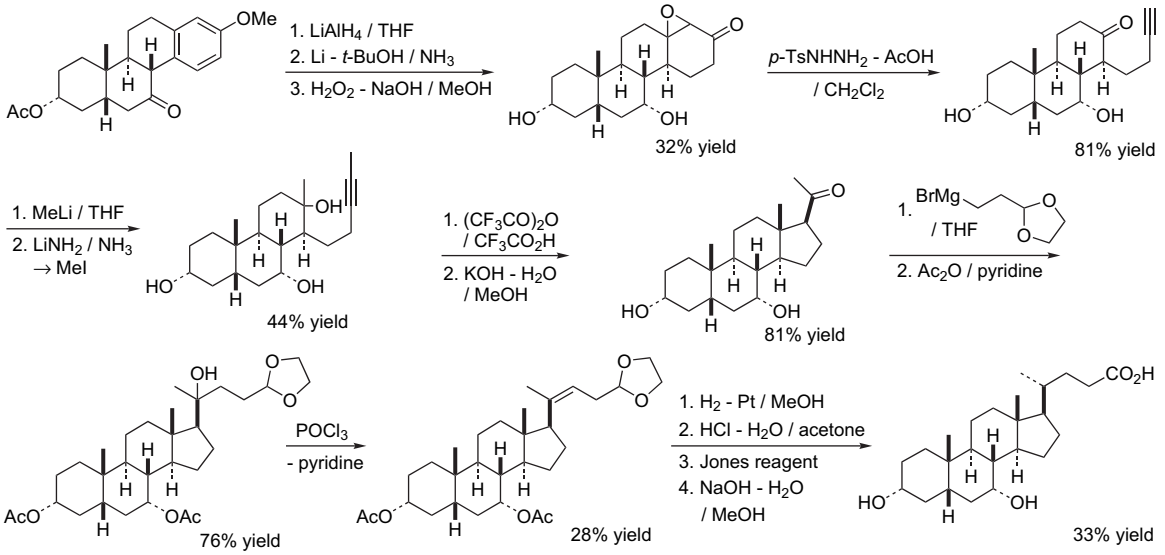
Scheme 93.



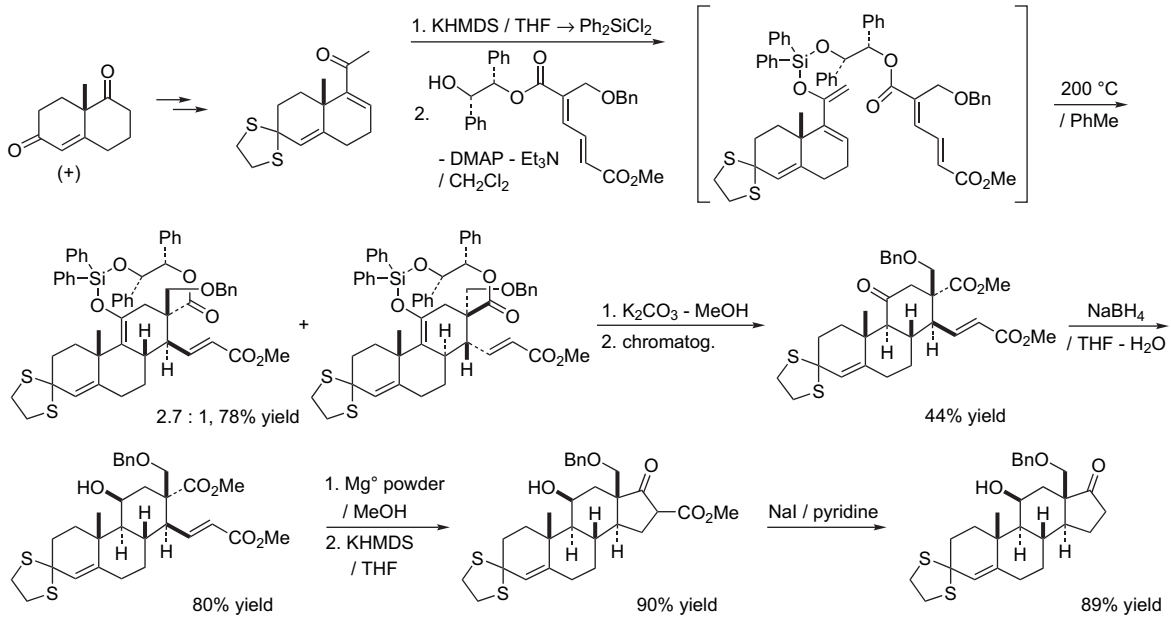
Scheme 94.

cycloaddition of the olefinic acylbenzocyclobutene, where the α-acetoxy group anchored on the cyclohexane ring directed the stereochemical course of the reaction (Scheme 94). Conversion to chenodeoxycholic acid required D-ring manipulations and stereoselective introduction of substituents (Scheme 95).[147]

A stereo- and regioselective tethered type 2 intramolecular Diels–Alder reaction was exploited by Shea and co-workers in their synthesis of an advanced tetracyclic steroid intermediate of the cortical hormone, (+)-aldosterone. The diene precursor was elaborated from (+)-Wieland–Miescher ketone using the procedure of Swaminathan and joined to the



Scheme 95.

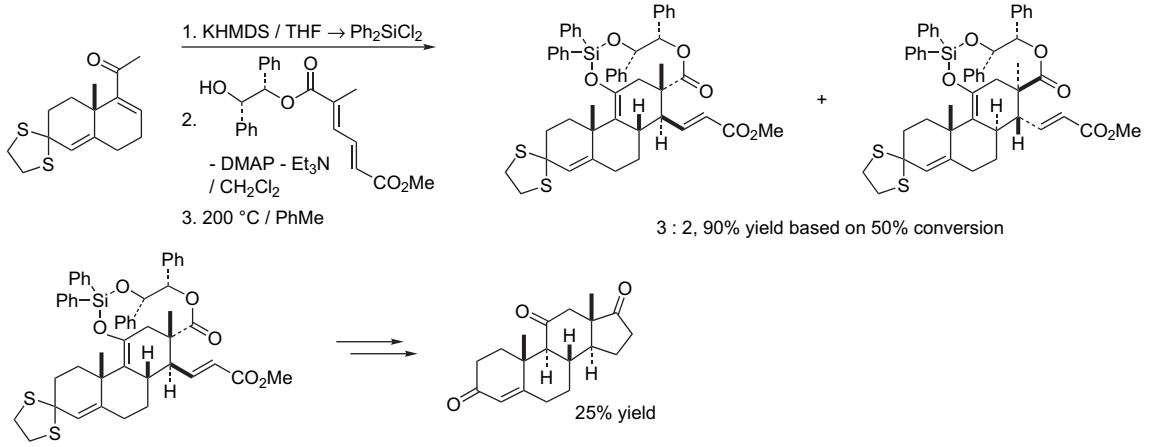


Scheme 96.

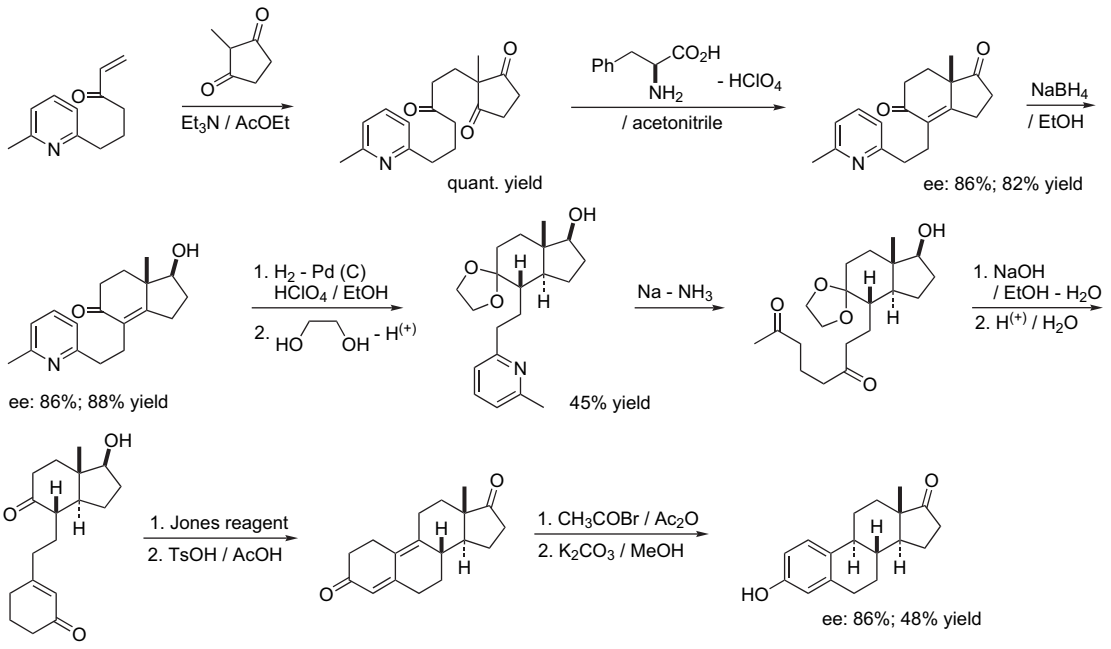
conjugated diester dienophile by a temporary chiral 1,2-diol silyl acetal tether, which provided control of the π-facial selectivity. The natural steroid stereochemistry of the four contiguous stereocenters C8, C9, C13, and C14 was controlled by the (*S*,*S*)-hydrobenzoin auxiliary, favoring an α-approach. Final construction of the D-ring involved a Dieckmann cyclization–demethoxycarbonylation sequence (Scheme 96).[148] Following the same strategy, a synthesis of the adrenalcorticosteroid, (+)-adrenosterone, was also realized by this group. However, in this case, the presence of the sole methyl group at C(13) compared to the bulkier benzyloxymethyl group influenced the selectivity of the cycloaddition process, which was down from 2.7:1 to 3:2 (Scheme 97).[149]

3.4.4. Enantioselective cyclization of other alkylcyclopentanediones. A number of approaches have made the Hajos–Parrish-type ketone a starting building block of choice for the construction of CD-steroid ring fragments, usually resulting from the addition of methylcyclopentanedione to a vinyl ketone derivative followed by enantioselective cyclization of the trione formed. In 1976, Danishefsky and Cain achieved the construction of the 8-ethylpicolyl indenedione through an L-phenylalanine-promoted asymmetric annulation under Eder, Sauer, and Wiechert conditions. A Birch reduction of the pyridine ring followed by cyclization in an alkaline medium led to the cyclohexenone A-ring, which underwent a vinylogous aldolization with the hydrindanone system and liberated 19-nor-steroids and estrone (Scheme 98).[150]

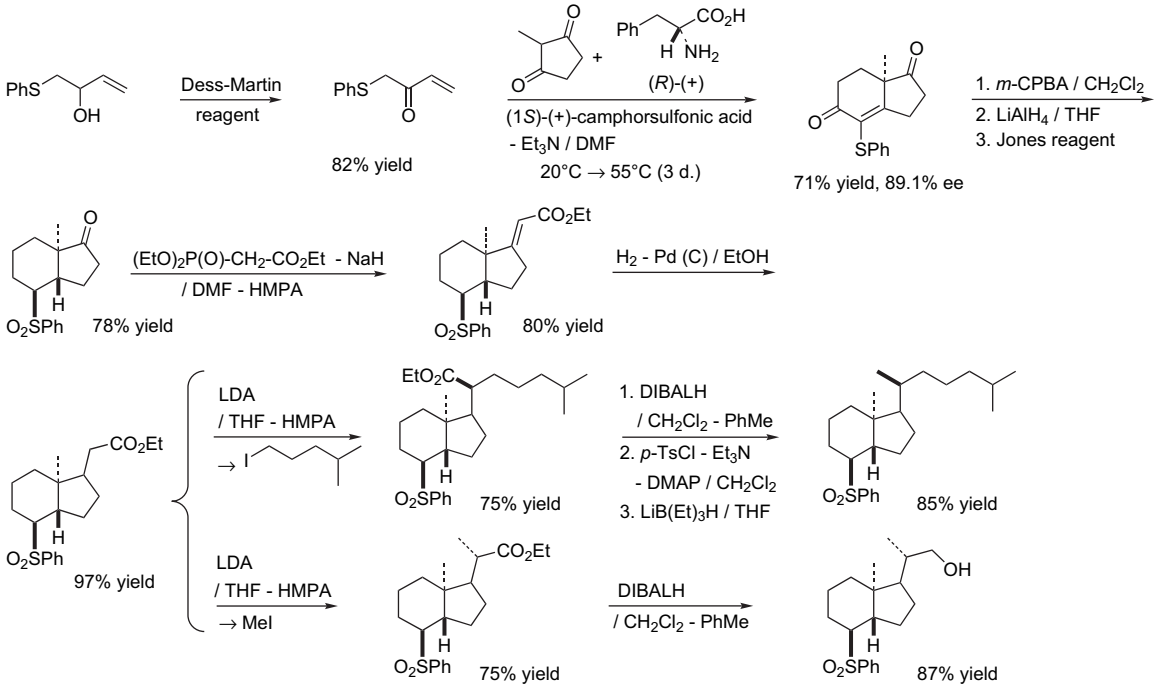
An interesting method for the introduction of a phenylsulfonyl group at the C(8)-position of *trans*-hydrindanes was developed by Wicha and was based on a phenylalanine-catalyzed enantioselective annulation of 2-methylcyclopenta-1,3-dione with phenylsulfanylmethyl vinyl ketone. By using the protocol described by Hagiwara and Uda (cf. Section 3.4.1) with (*S*)-(−)-phenylalanine, (*R*)-thioindenedione was obtained with an ee up to 95.6% after recrystallization. From α-alkylation of the saturated ester, Wicha could build the side chain and obtain two essential synthons for the synthesis of *ent*-vitamin D, in which the sulfonyl group



Scheme 97.



Scheme 98.



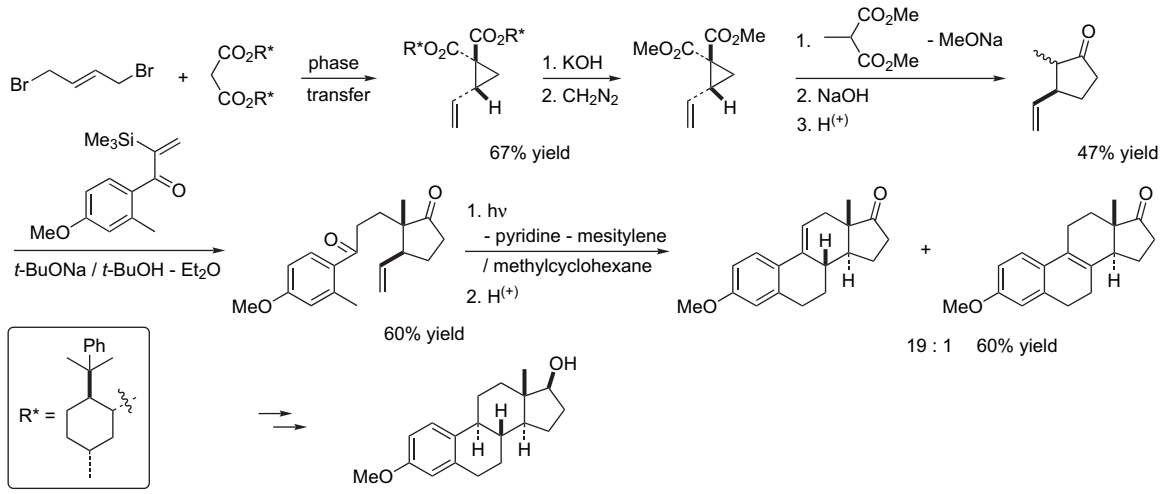
Scheme 99.

could serve to couple the Northern portion building block to an A-ring fragment via a Julia olefination (Scheme 99).[151]

4. Use of chiral auxiliaries, chiral metal–ligand complexes or chiral bases

4.1. Use of chiral auxiliaries

Several new routes to enantiomerically enriched steroids have appeared recently employing chiral auxiliaries to introduce chirality. In one example, during the total synthesis of 19-nor-steroids, Quinkert observed that an $S_{cN}2'$ reaction of 1,4-dibromobut-2-ene with (−)-bis(8-phenylmenthyl) malonate under phase-transfer conditions led to the vinylcyclopropane as a 98:2 mixture of diastereoisomers. This latter cycloalkane was then converted into the enantiomerically enriched 2-methyl-3-vinyl-cyclopentanone through an annulation process promoted by malonic ester/NaOMe. The diastereoselective Michael addition of its enolate to a silylated aryl vinyl ketone generated a steroid precursor, which was readily engaged in a tandem



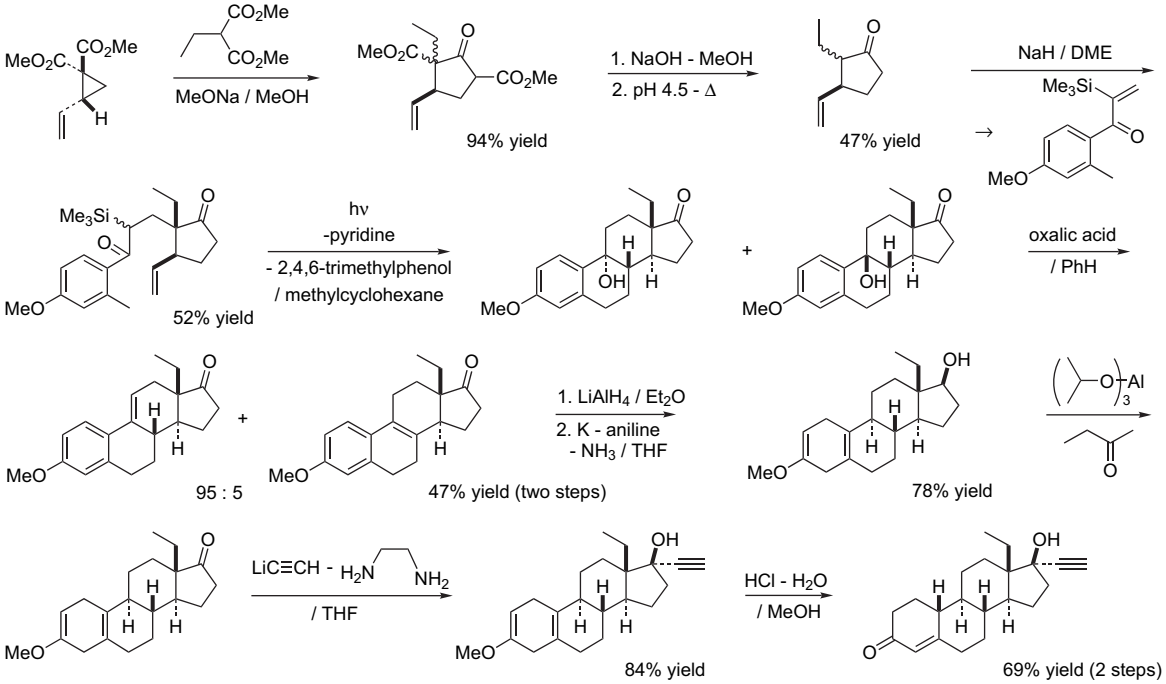
Scheme 100.

photo-enolization–intramolecular Diels–Alder cycloaddition of the *o*-quinodimethane intermediate. The dehydrated cycloadducts with a trans-fused CD-ring were isolated in 60% yield and functional-group transformations achieved the preparation of 19-nor-steroids (Scheme 100).[152] Three years later, the same authors applied this strategy to the synthesis of (−)-norgestrel and (−)-norethindrone, as depicted in Scheme 101.[153]

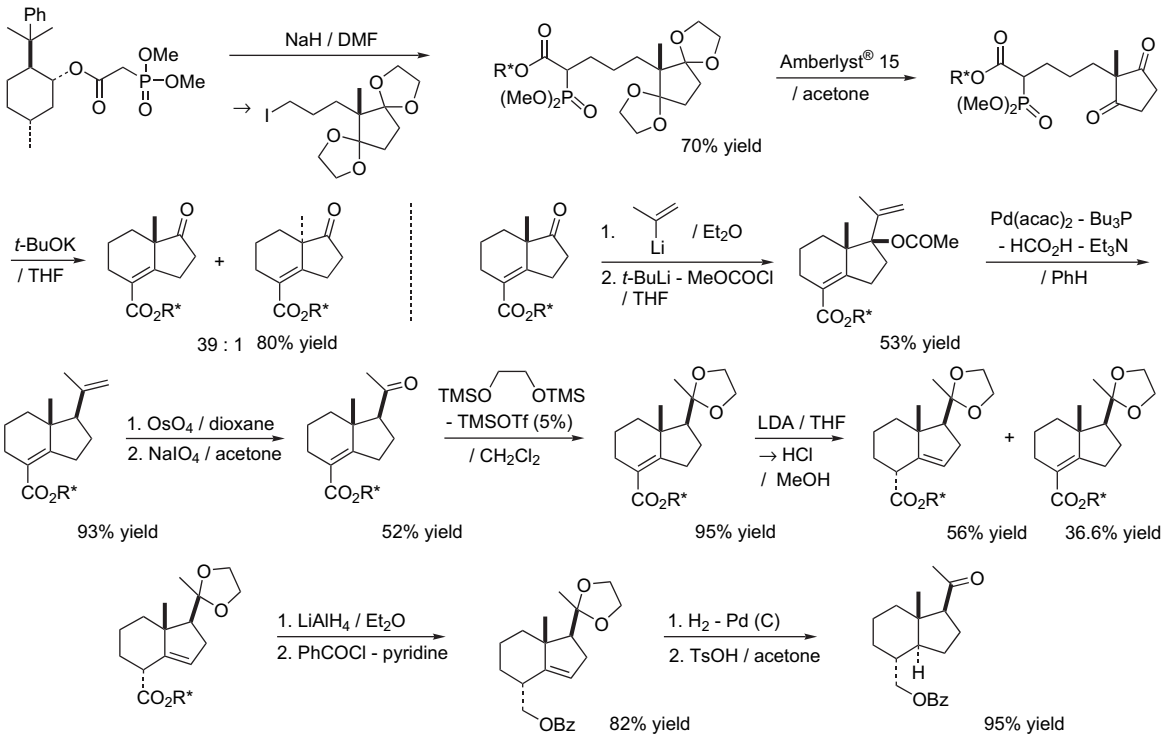
An asymmetric cyclization by intramolecular Horner–Emmons olefination of 1,3-cyclopentanedione leading to the CD-ring system of vitamin D was reported by Mandai and co-workers. Desymmetrization of the dicarbonyl compound was realized by the use of a chiral phosphono ester, possessing (−)-8-phenylmenthol as an optically active auxiliary, with an excellent diastereoselectivity. The trans BC-ring junction was achieved by deconjugation of the α,β-unsaturated ester to its β,γ-counterpart and subsequent catalytic hydrogenation of the olefin (Scheme 102).[154]

During his work directed toward the total synthesis of steroids via intramolecular Diels–Alder reactions of *o*-quinodimethanes, Fukumoto investigated the thermolysis of the corresponding chiral benzocyclobutenes, which have a C_2-symmetric acetal moiety as a chiral auxiliary. The des-AB-aromatic steroid *trans*-benzoperhydroindans were formed with a high diastereoselectivity and an enantiomeric excess up to 36% (Scheme 103).[155]

In their approach to the first synthesis of (+)-cortisone, Fukumoto and co-workers started from the (*R*)-(+)-pulegone-derived chiral 1,3-oxathiane reported by Eliel,[156] which was converted into the diastereomerically pure equatorial 2-acyl derivative. Grignard addition gave the tertiary



Scheme 101.



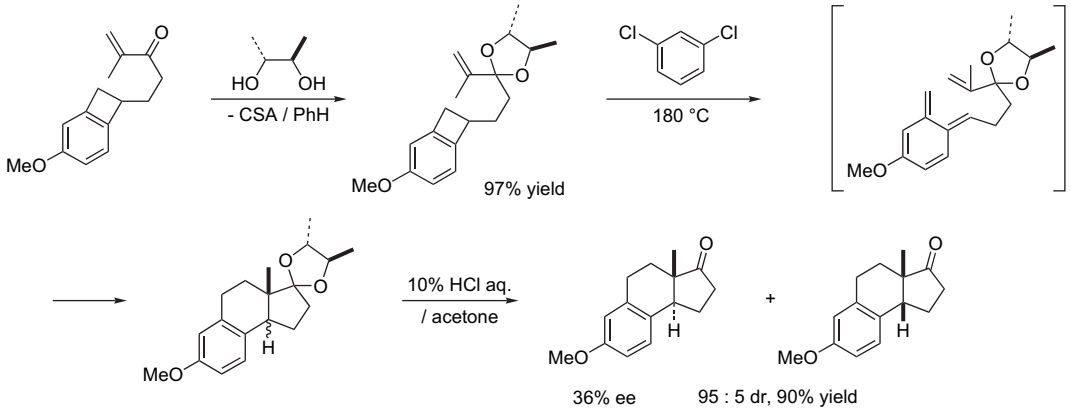
Scheme 102.

isopropenyl alcohol as a unique stereoisomer and intramolecular Diels–Alder cycloaddition of the olefinic benzocyclobutene generated the unique *trans* A-nor-B-aromatic steroid. The *exo*-transition state is favored, due to steric interactions that allowed the formation of the 18β-methyl cycloadduct isomer. The natural cortisone was then elaborated from this tricyclic intermediate (Scheme 104).[157]

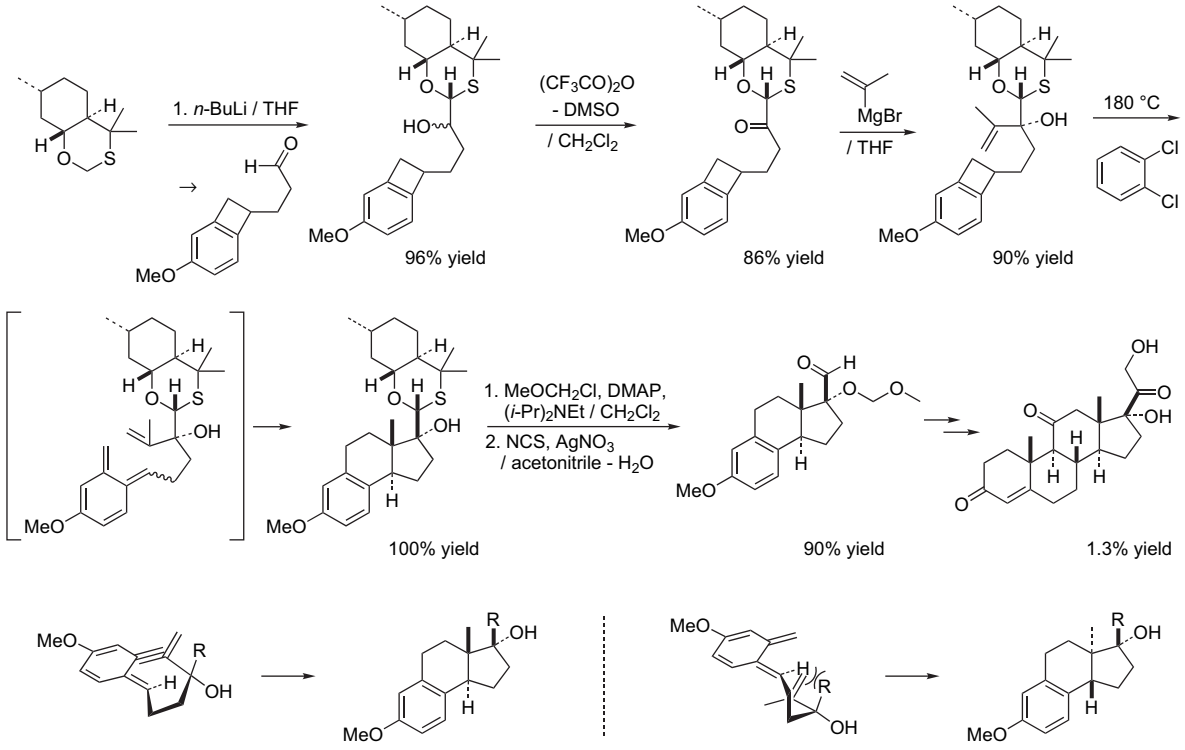
To introduce the asymmetry, Nemoto and co-workers replaced the chiral 1,3-oxathiane auxiliary by a dimethyldioxolane moiety, accessible from the natural chiral source, D-mannitol. Diastereoselective vinyl Grignard addition to the chiral *O*-isopropylideneglyceroketone prepared from 1-ethynylbenzocyclobutene and protected (*R*)-glyceraldehyde, thermal electrocyclic ring opening and subsequent intramolecular [4+2] cycloaddition yielded the target tricyclic steroid-like skeleton having a trans-relative configuration (Scheme 105).[158]

Fukumoto and co-workers reported the preparation of an A-nor B-trienic 18,18,18-trifluorosteroid and its enantiomer as potential intermediates for the synthesis of 18,18,18-trifluorosteroids. The construction of the tricyclic precursor involved ring closure by a Diels–Alder reaction of a chiral olefinic benzocyclobutene. This latter cycloalkene was obtained via a diastereoselective aldol reaction of a (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone-derived unsaturated imide with 4-methoxybenzocyclobutenyl-1-acetaldehyde (Scheme 106). The enantiomeric fluorinated compound was prepared following the same strategy by using (4*S*)-4-benzyl-2-oxazolidinone as a chiral auxiliary (Scheme 107).[159]

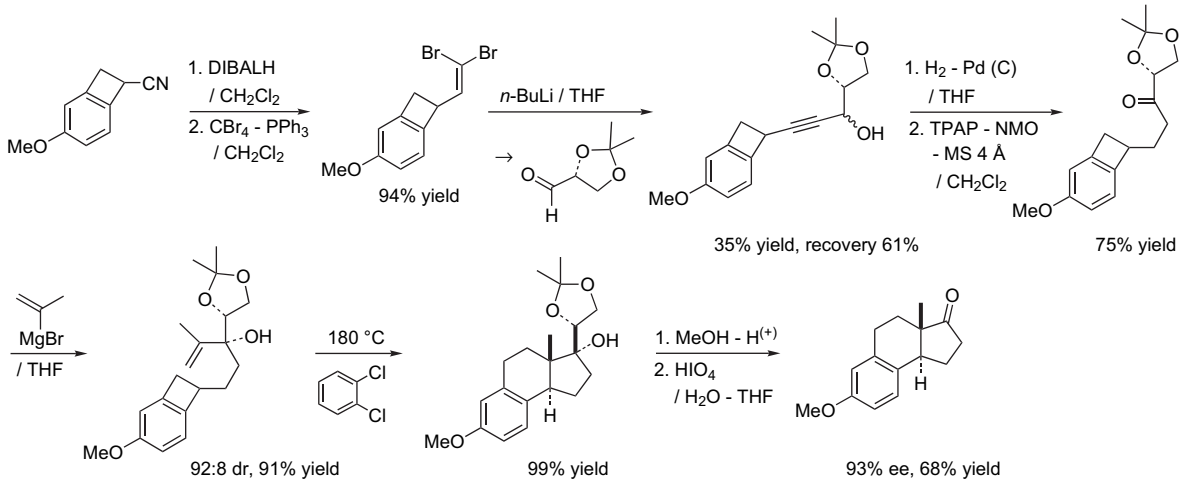
An Evans-type *syn*-selective asymmetric aldol reaction of α-bromoacrolein with the boron enolate of 3-chloroacetyl-4(*S*)-isopropyl oxazolidinone and a Pd(0)-mediated intramolecular Heck-type reaction of a vinyl bromide onto an



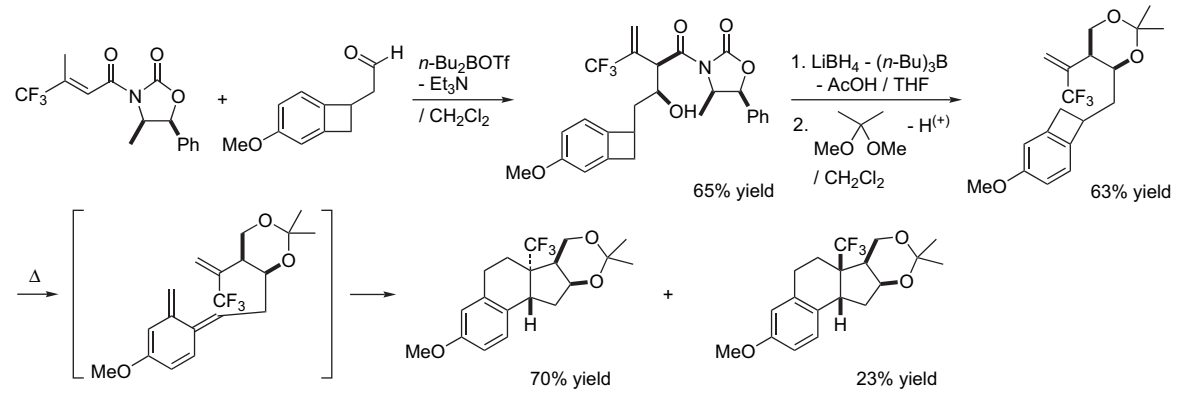
Scheme 103.



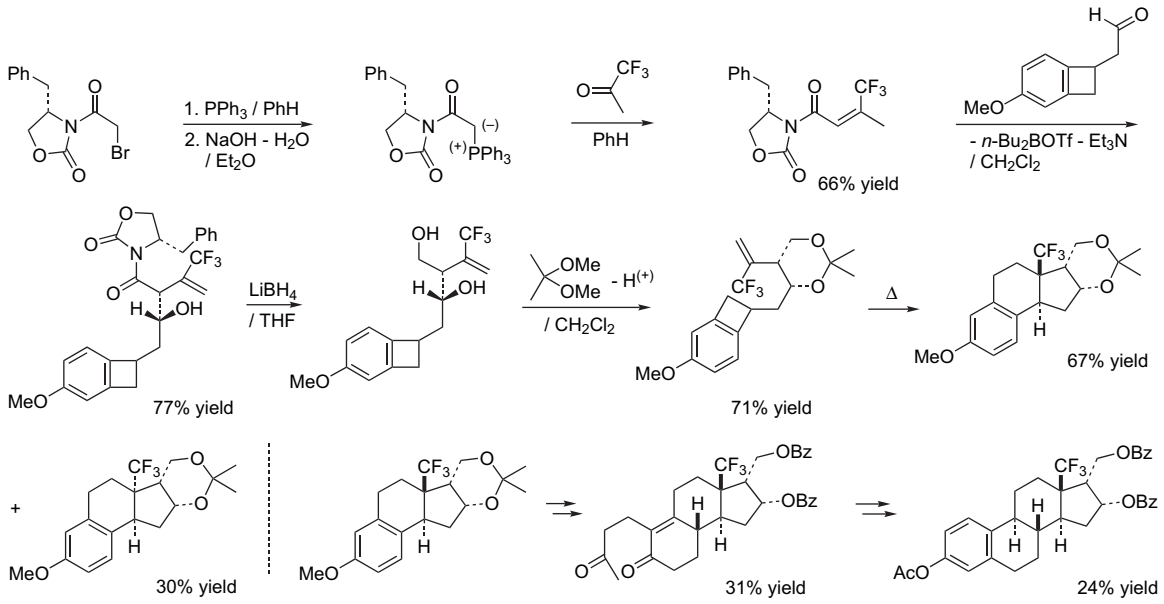
Scheme 104.



Scheme 105.



Scheme 106.

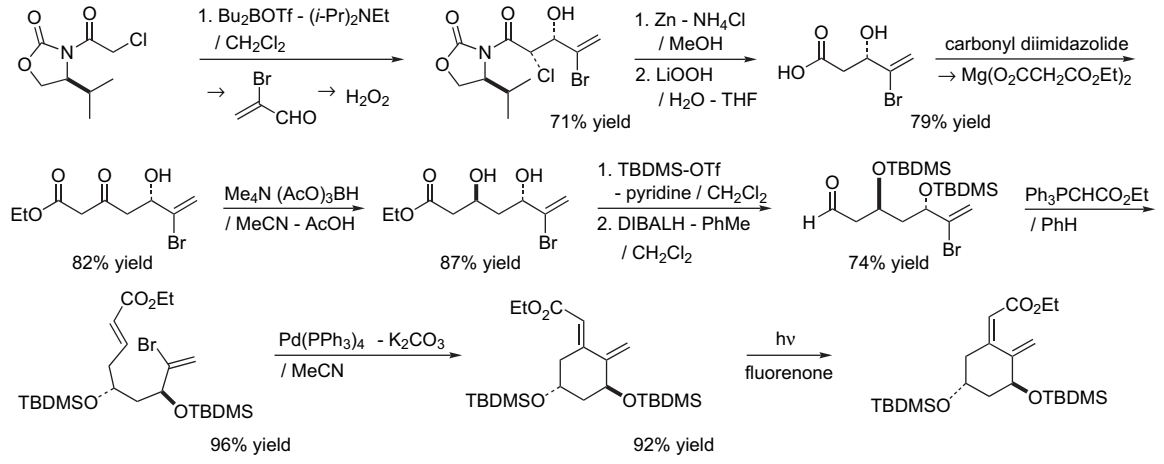


Scheme 107.

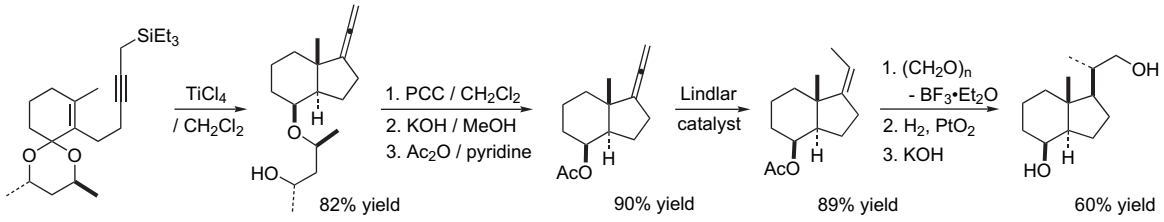
α,β-unsaturated ester were used by Chen and Crich to synthesize the diene ester A-ring of the 1α,25-dihydroxyvitamin D_3 (Scheme 108).[160]

During their studies on polyene cyclization by electrophilic activation, Johnson and co-workers constructed the Inhoffen–Lythgoe diol by means of an asymmetric Lewis acid-catalyzed bicyclization of an optically active enyne acetal. The chiral auxiliary was removed by oxidation and base-assisted retro-Michael elimination. Semi-hydrogenation of the terminal double bond of the allene occurred from the more exposed face and gave the *Z*-isomer. A tandem ene reaction and stereospecific hydrogenation were carried out in order to complete the synthesis (Scheme 109).[161]

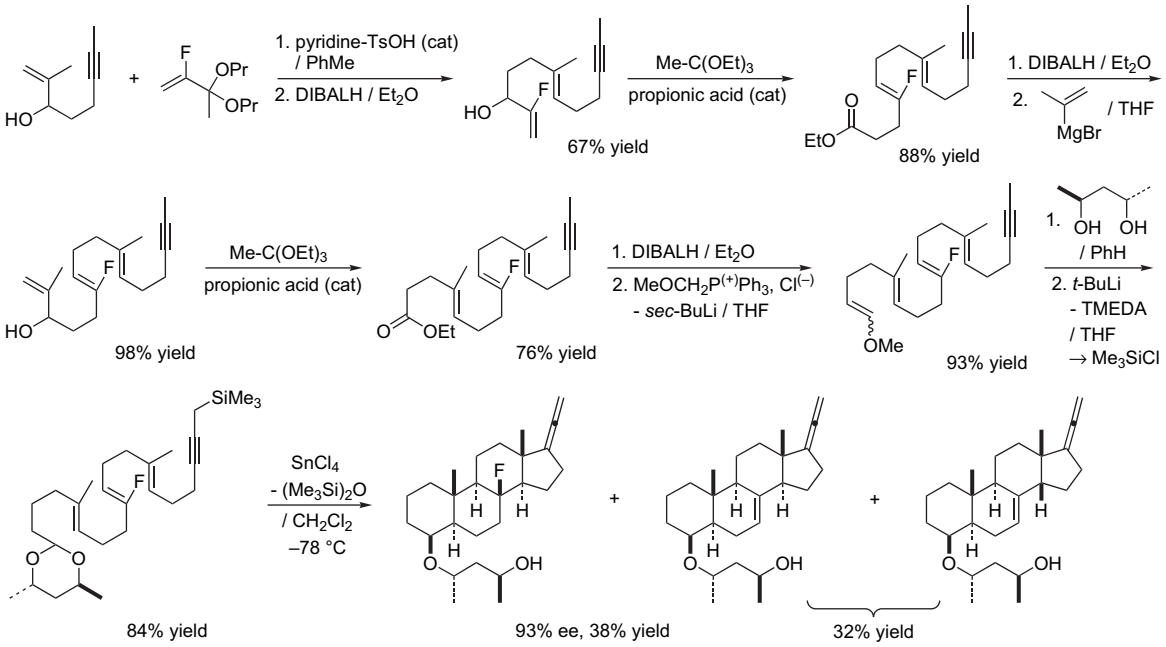
Afterward, a stereoselective cation-induced biomimetic polyenic tetracyclization of an acyclic tetraenic acetal was exploited by Johnson and co-workers in their synthesis of optically active steroids. The (*S*,*S*)-2,4-pentanediol-derived chiral acetal controlled the stereochemistry of the cascade



Scheme 108.



Scheme 109.



Scheme 110.

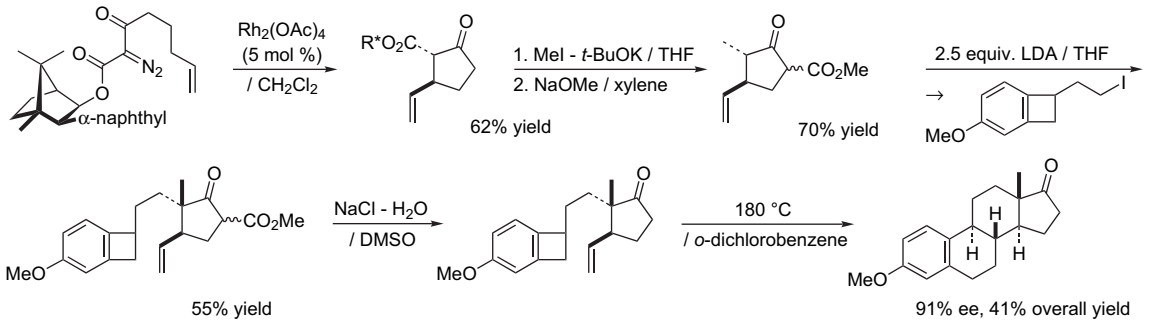
process and the presence of a fluorine atom at the pro-C(8) center stabilized the intermediate carbocation that enhanced the effectiveness of the reaction. A fluorotetracycle with natural steroid configuration was obtained in 38% yield and 93% ee, together with a mixture of alkenes (32%) (Scheme 110).[162]

An enantioselective construction of a functionalized cyclopentane derivative, employed as a D-ring precursor of (+)-estrone methyl ether, was reported by Taber and co-workers. The reaction sequence included a rhodium(III)-mediated diastereoselective intramolecular CH insertion of a chiral bis-homoallyl α-diazo-β-keto ester, prepared starting from (1*S*,3*S*)-*exo*-hydroxy-2(*S*)-*exo*-naphthyl-bornane, followed by a sequential α-methylation, 1,3-ester shift, and dianion alkylation with 2-(4-methoxybenzocyclobutenyl)-ethyl iodide. The corresponding decarbomethoxylated compound underwent an intramolecular Diels–Alder cycloaddition to give (+)-estrone methyl ether (Scheme 111).[163]

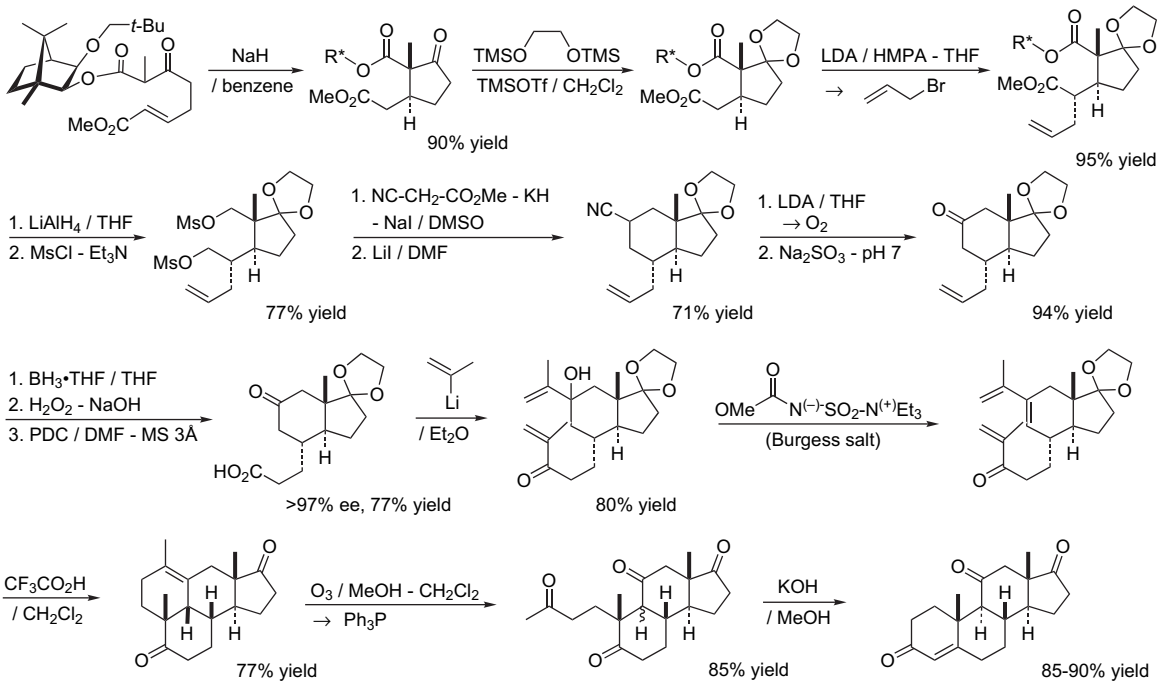
Stork and Saccomano showed that intramolecular Michael addition of the borneol-derived β-keto ester anion to an α,β-unsaturated ester produced a trisubstituted *trans*-cyclopentanone, useful for the construction of the D-ring of 11-ketosteroids and with the correct absolute configuration.[164]

Completion of the C-ring was realized by dialkylation of methyl cyanoacetate, leading to the insertion of the C(11) carbonyl. The Diels–Alder cyclization of the elaborated trienone with concomitant deprotection of the C(17) ketone was effected with trifluoroacetic acid and provided the tetracyclic intermediate,[165] which was converted into adrenosterone upon the usual ozonolysis–cyclization sequence (Scheme 112).[166]

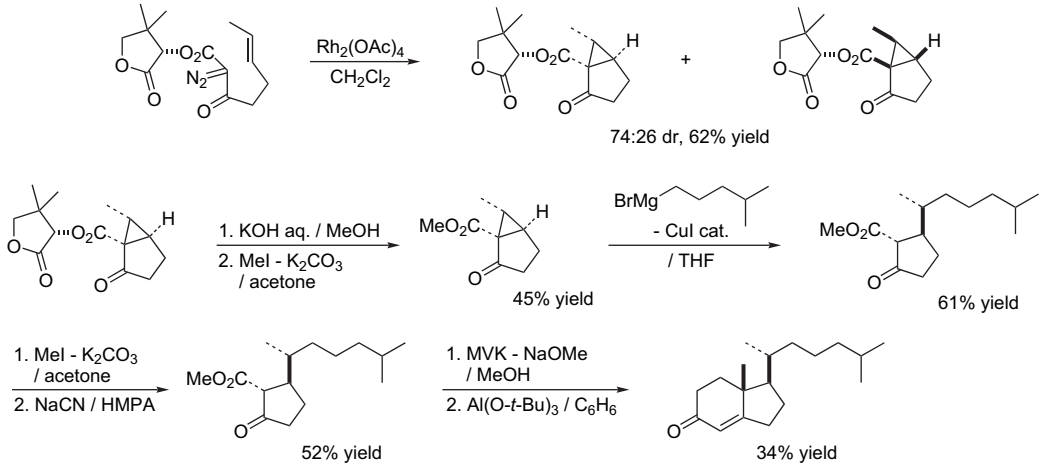
A rhodium(II) acetate complex-mediated intramolecular cyclopropanation of an unsaturated α-diazo-β-keto ester bearing (*S*)-pantolactone was the key step in the synthesis of non-racemic vitamin D_3 CD-ring synthons developed by Tanimori and co-workers. Addition of a Grignard reagent catalyzed by copper iodide was carried out on the major diastereoisomer of the newly formed bicyclo[3.1.0]hexane and was shown to proceed regioselectively at the methylated carbon through cyclopropane ring opening. This manipulation allowed the direct introduction of the vitamin D_3 side chain. A series of routine reactions furnished the previously characterized cyclopentanone, which underwent a Robinson-type annulation. Using the same reaction sequence, the opposite diastereomer was converted into the *ent*-vitamin CD-ring synthon (Scheme 113).[68a]



Scheme 111.



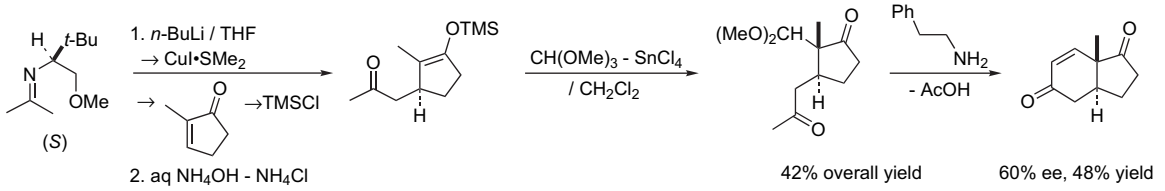
Scheme 112.



Scheme 113.

A short asymmetric approach to the construction of a *trans*-dihydrindanedione was reported by Tsuji and co-workers. Their synthetic strategy was centered on the formation of a copper azaenolate, obtained by a sequential lithiation of an acetone imine of (*R*)-*tert*-leucinol methyl ether, copper(I) transmetallation, and its conjugate addition to 2-methyl-cyclopentenone. A tin(IV) chloride-mediated reaction of silyl enol ether with trimethyl orthoformate was suggested for the introduction of the formyl group and a subsequent acidic aldol condensation generated the indenedione in 60% ee (Scheme 114).[167]

As part of their studies on radical cyclization of haloacetals, Stork proposed an alternative route to *trans*-hydrindane



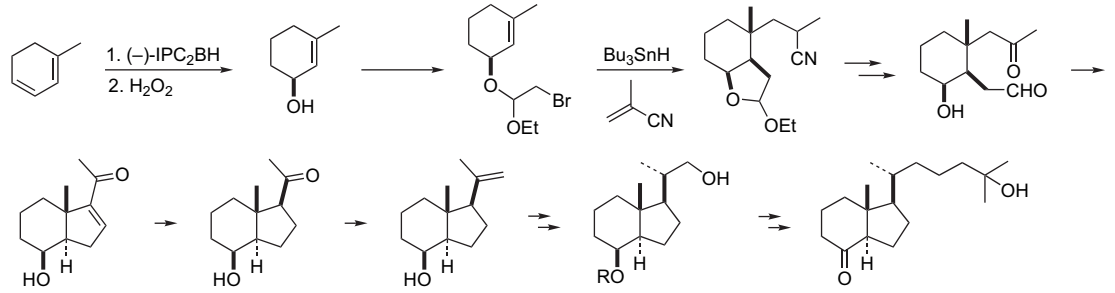
Scheme 114.

steroid precursors, and particularly the CD system of D vitamins such as calcitriol. The construction of the Windaus–Grundmann-type ketone hydroxylated at C(25) was undertaken via a tandem radical cyclization of a mixed bromoacetal derived from the optically active 3-methyl-2-cyclohexenol and trapping of the transient carbon radical by acrylonitrile that controlled the formation of the stereogenic center at C(14) and the trans-junction, respectively. One of the best-known methods for preparing the starting cycloalkenol was the asymmetric hydroboration of 1-methyl-1,4-cyclohexadiene with diisopinocampheylborane. Ring closure of the D-ring and introduction of the side chain using standard transformations completed the synthesis. However, the absence of reaction details makes these results unworkable (Scheme 115).[168]

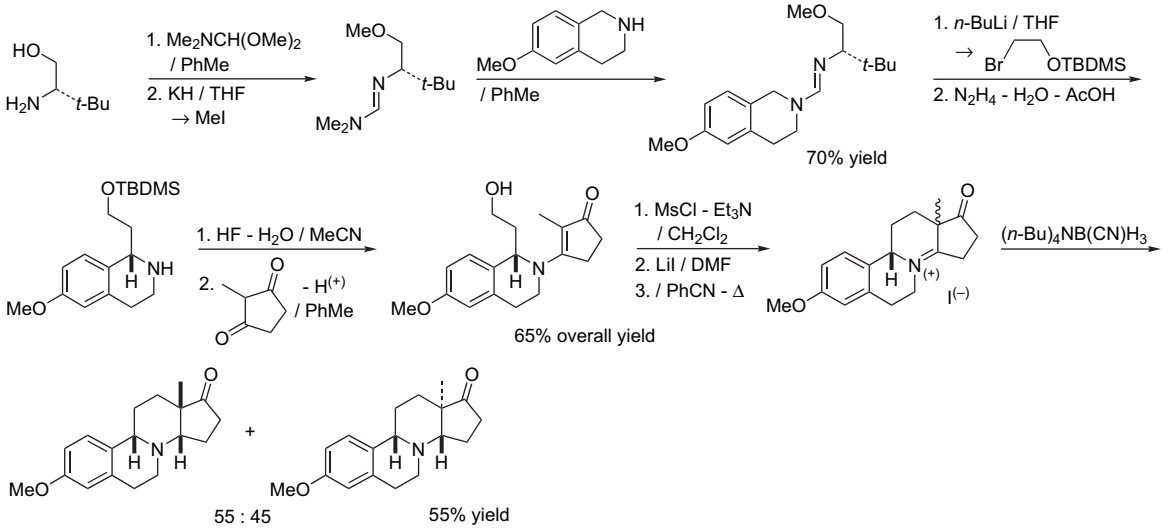
The synthesis of (−)-8-azaestrone by Meyers and Elworthy featured the asymmetric alkylation of (*S*)-*tert*-leucinol-derived formamidine isoquinoline with a β-bromo ether with 94% ee, hydrazinolysis of the chiral auxiliary, enamine formation with 2-methyl-1,3-cyclopentanedione to insert the D-ring moiety followed by cyclization to the tetracyclic system through intramolecular alkylation, and reduction of the intermediate iminium salt by treatment with tetrabutylammonium cyanoborohydride (Scheme 116).[169]

An interesting ABC intermediate for steroid synthesis was proposed by d'Angelo and co-workers. Their synthetic sequence started with the preparation of an optically active phenanthrone through an asymmetric Michael addition process involving chiral imines. Condensation of the secondary enamine, obtained from both 1-methyl-2-tetralone and (*S*)-(−)-α-methylbenzylamine, with methyl vinyl ketone yielded a bridged ketol, which was then transformed into the target (*S*)-phenanthrone in 80% yield with 93% ee. Simple functional-group transformations, in which the trans AB-ring junction was established during the enone reduction upon Birch conditions and the trans BC-ring junction by hydrogenation of the phenol unit and epimerization, completed the synthesis of the *trans-anti-trans* diketone (Scheme 117).[170]

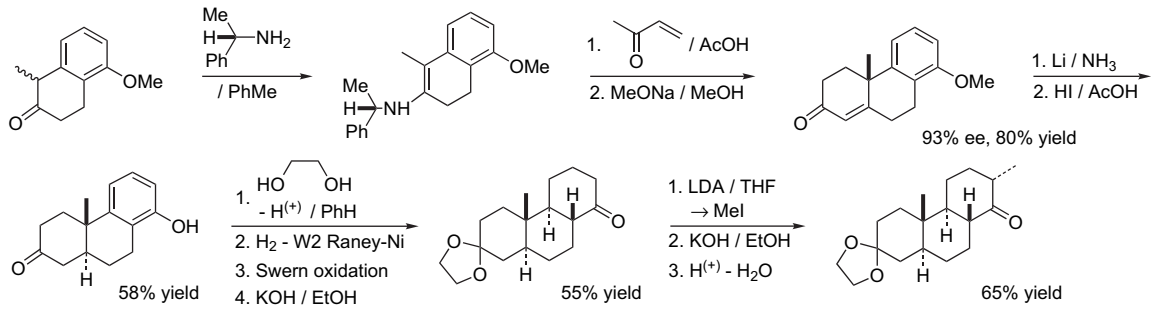
For the synthesis of 1α,25-dihydroxyvitamin D_3, Wilson developed an attractive route to a new acetylenic A-ring precursor involving a rhodium-catalyzed intramolecular cyclopropanation of a homoallyl α-diazo-β-keto ester. The introduction of the chirality was ensured by the presence of the chiral auxiliary, 1(*S*)-3(*S*)-*exo*-hydroxy-2(*S*)-*exo*-naphthyl-bornane. After recrystallization and further transformations, the resulting bicyclo[3.1.0]hexan-2-one was converted into the corresponding enyne through vinyl bromide formation, and then addition of the lithium acetylide to 25-hydroxy Windaus–Grundmann ketone formed the cyclopropyl-substituted propargylic alcohol. Its LAH reduction to a vinylogue of a cyclopropyl alcohol and acid-catalyzed solvolysis via allylic cation formation afforded calcitriol as a unique isomer in 64% yield (Scheme 118).[171]



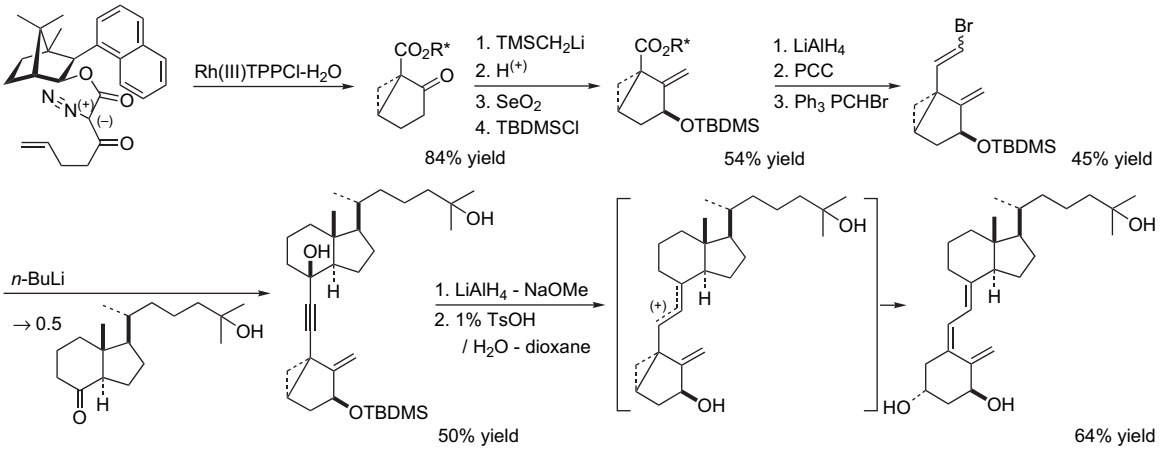
Scheme 115.



Scheme 116.



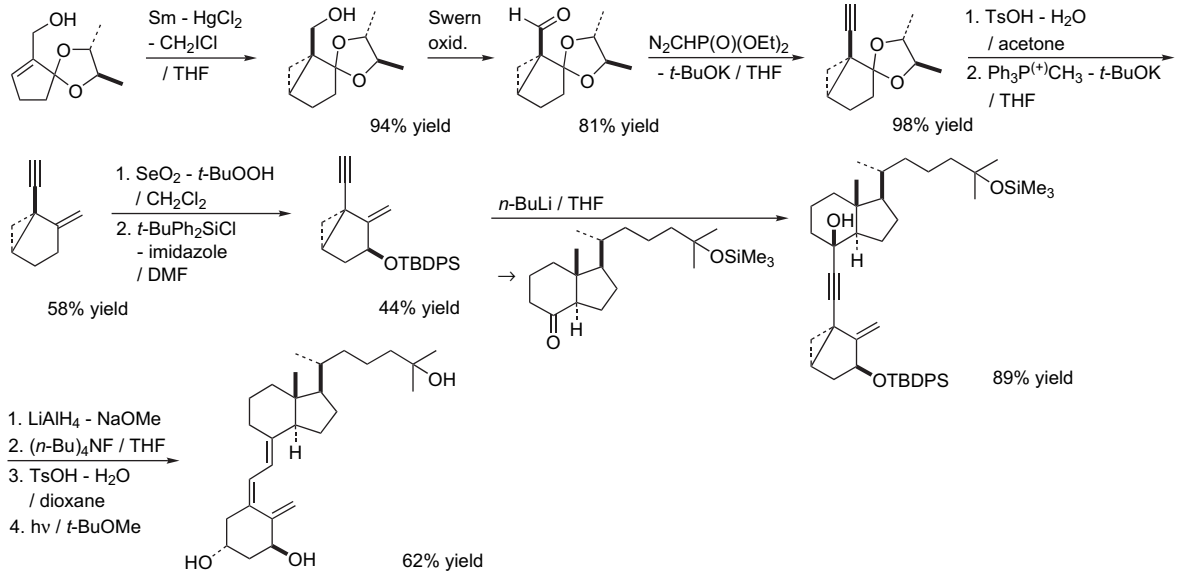
Scheme 117.



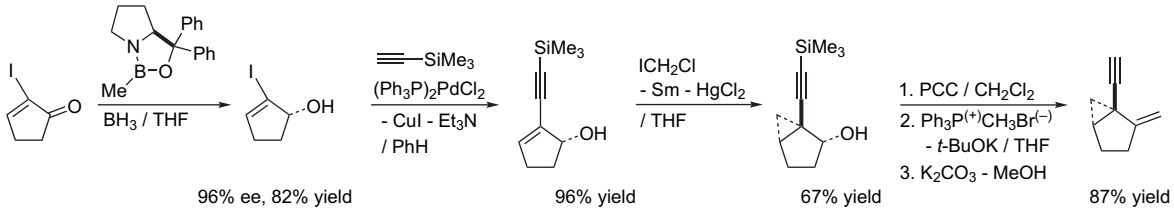
Scheme 118.

A similar enantiomerically pure enyne, obtained either by diastereoselective cyclopropanation of allylic alcohol or through chiral allylic alcohol-directed cyclopropanation under Molander's conditions, was synthesized by Uskoković. The chirality was introduced by the (*R*,*R*)-2,3-butanediol ketal moiety (Scheme 119) or from (1*R*)-2-iodo-cyclopenten-1-ol, generated by Corey's chiral oxazaborolidine reduction of the corresponding ketone (Scheme 120). Thus, these building blocks were readily engaged in the elaboration of calcitriol.[172]

A cyclopentenone sulfoxide, (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone, the chirality of which is ensured by the presence of the enantiomerically pure sulfoxide unit, was used by Posner and Switzer as a Michael acceptor. Asymmetric



Scheme 119.



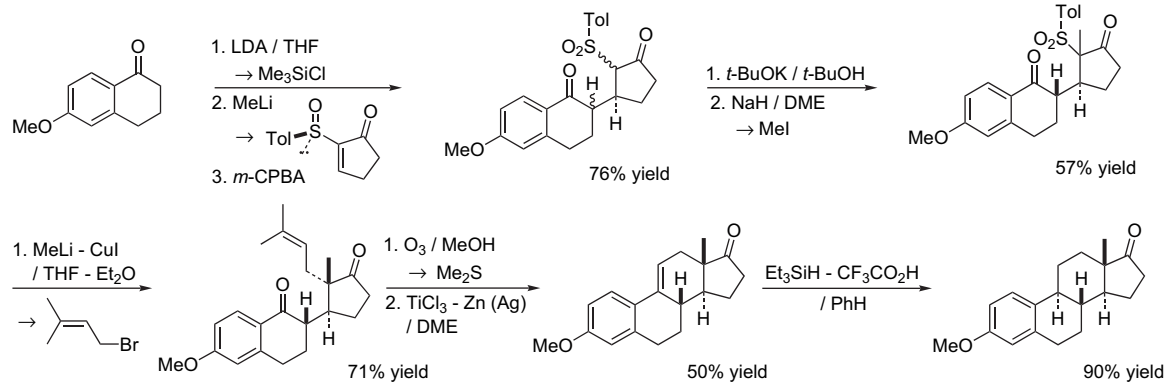
Scheme 120.

conjugate addition of methoxytetralone enolate led to a mixture of diastereoisomers simplified by oxidation of the sulfinyl group to sulfone. Further transformations including a McMurry reductive cyclization closed the C-ring and achieved the construction of the estrone skeleton with a natural configuration (Scheme 121).[173]

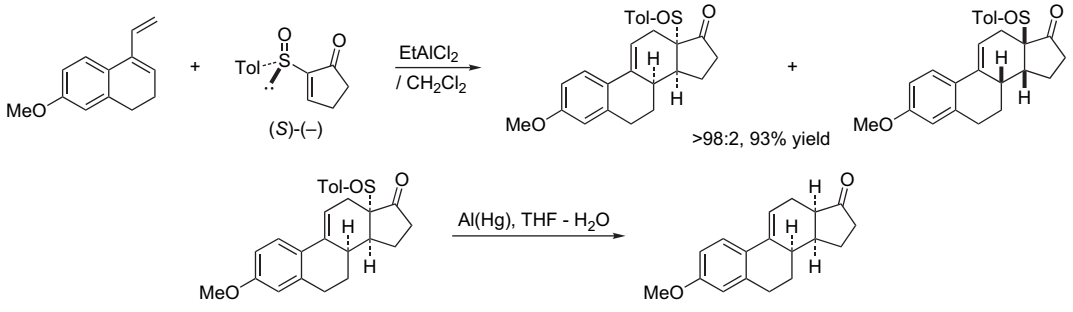
At the end of the 1930s, Dane's diene or 6-methoxy-1-vinyl-3,4-dihydronaphthalene was proposed as a useful and convenient synthon for the synthesis of estrone.[5] The same diene was employed by Carretero and co-workers in a regio- and diastereoselective Diels–Alder reaction with the previous optically pure β-keto sulfoxide. The exclusive formation of the *endo*-product was realized at −25 °C in DCM with $EtAlCl_2$ as a catalyst and the subsequent reductive elimination of the sulfinyl group with Al(Hg) in THF/H_2O. In this case, the CD bicycle cis-junction was preserved, leading to *syn*,*cis*-steroid skeletons (Scheme 122).[174]

As useful steroid intermediates, optically pure 2,3-disubstituted cyclopentanone and cyclopentanone enol silyl ether were synthesized by Posner and co-workers from zinc bromide-mediated vinyl conjugate addition to the chiral cyclopentenone sulfoxide and reductive cleavage of the sulfinyl group. Alkylation of these compounds by a suitable *o*-quinodimethane precursor followed by intramolecular Diels–Alder reaction should afford 19-nor-steroid cycloadducts (Scheme 123).[175]

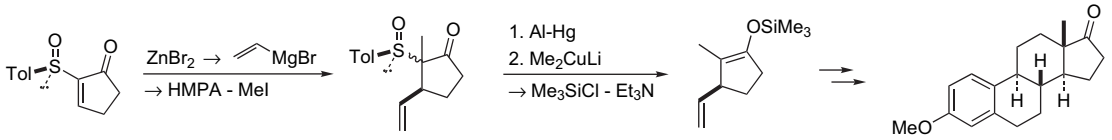
Diastereoselective addition of (*E*)- and (*Z*)-crotylsilanes to chiral 2-alkoxycarbonyl-2-cyclopentenones was reported by Pan and Tokoroyama and used for the preparation of



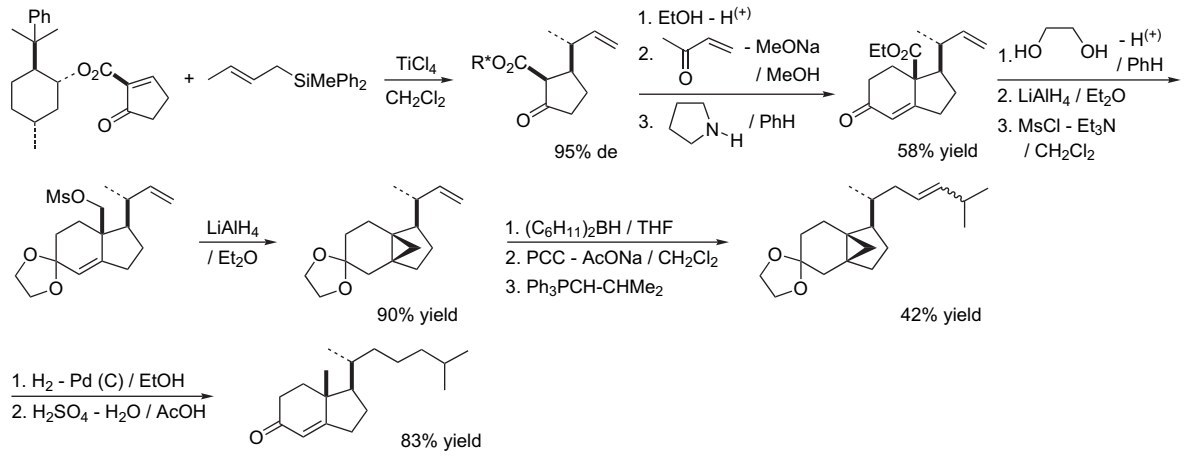
Scheme 121.



Scheme 122.



Scheme 123.



Scheme 124.

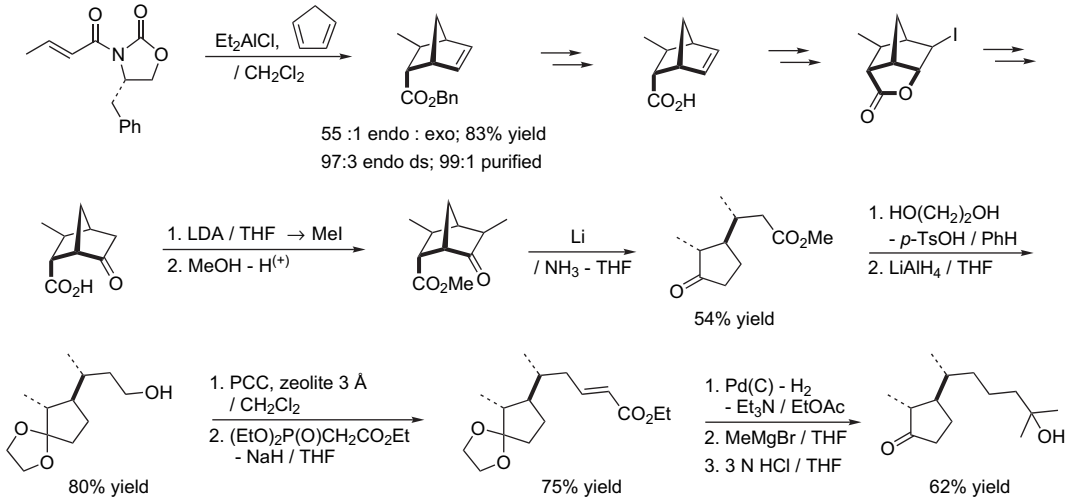
enantiopure des-AB-cholest-8-en-one, a valuable intermediate for vitamin D_3 synthesis. The reaction between 2-[(1*S*, 2*R*,5*S*)-(+)-8-phenyl-menthoxycarbonyl]-2-cyclopentenone and *E*-methydiphenylcrotylsilane afforded the disubstituted cyclopentanone with excellent diastereoface selectivity (3*R*) and *erythro* extracyclic selectivity. A construction of the C-ring by Robinson annulation, degradation of the menthoxy-carbonyl group, and extension of the side chain completed the synthesis of the chiral steroid CD-ring synthon (Scheme 124).[176]

Shimizu and co-workers have synthesized a potent 25-hydroxyvitamin D_3 chiral cyclopentenone synthon by reductive cleavage of a norbornan-6-one-2-carboxylate, as described in Scheme 125. The optically pure norbornane skeleton was constructed by an asymmetric Diels–Alder cycloaddition reaction with a chiral α,β-unsaturated *N*-acyl-oxazolidinone.[177]

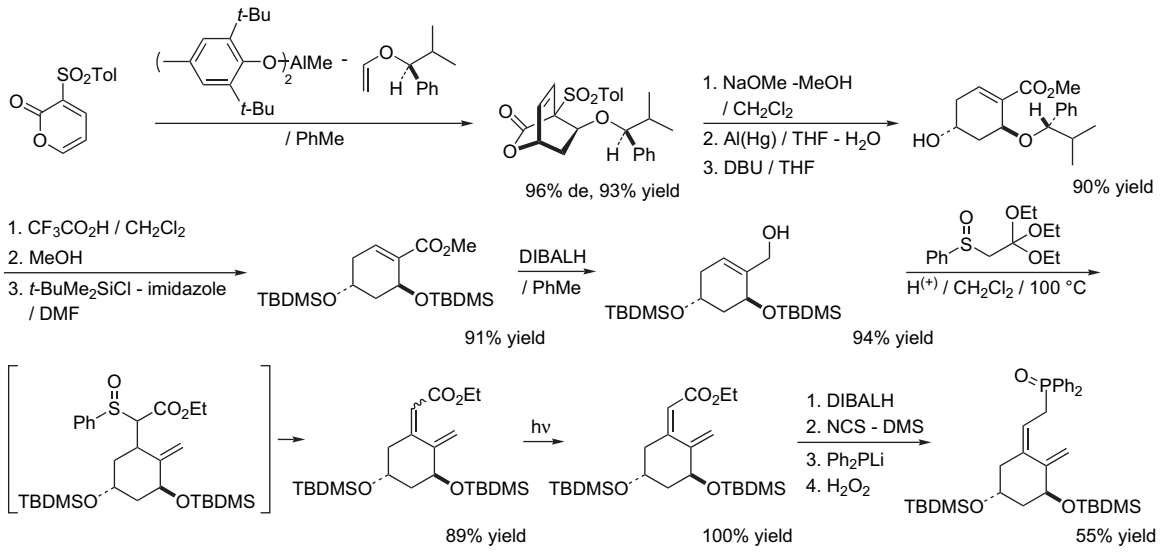
A clever synthesis of Lythgoe allylic phosphine oxide and its most important dienoate intermediate was proposed by Posner and Kinter. The key stage was a Yamamoto's 'MAD' Lewis acid-promoted highly stereocontrolled [4+2] cycloaddition between 3-sulfonyl-2-pyrone and an enantiomerically pure vinyl ether. The resulting bicyclic lactone was isolated in 93% yield with a 98:2 ratio of *endo* diastereoisomers. A sequence of trivial transformations resulted in the formation of a correctly substituted allylic alcohol. The C(6) and C(7) carbon atoms were introduced together via a new sulfinyl orthoester Claisen [3,3]-sigmatropic rearrangement and subsequent pyrolytic 1,2-elimination of sulfoxide (Scheme 126).[178]

Another route to the non-rearranged intermediate allylic alcohol was found by Posner and co-workers by exploiting the Diels–Alder reaction with 2-pyrones and vinylic ethers, which involved a double stereodifferentiation process. Cycloaddition of enantiomerically pure 2-pyrone (*S*)-lactate with the appropriately matched enantiomeric form of the NMR shift reagent, (−)-Pr(hfc)$_3$, produced almost exclusively the two bicyclic *endo* lactones with 96% de (Scheme 127).[179] Similar results were obtained by using (*R*)-(+)-Binol-TiCl$_2$(O-*i*-Pr)$_2$ as a chiral non-racemic Lewis acid with the commercially available methyl-2-pyranone-3-carboxylate and various enol ethers (Scheme 128).[180]

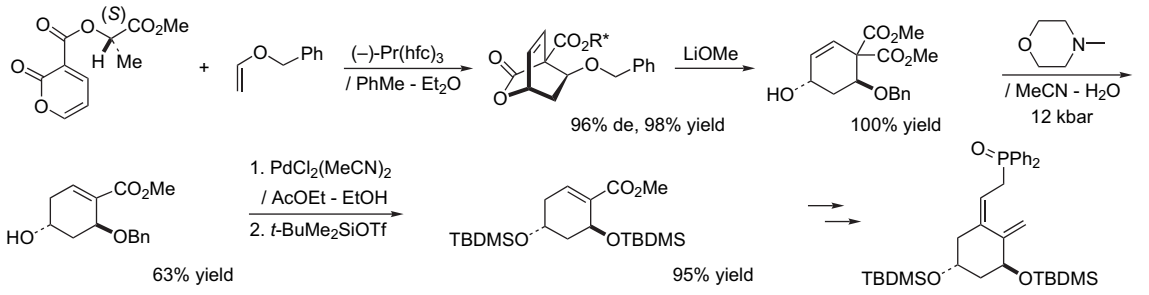
As part of a program directed toward the synthesis of C(2)-substituted vitamin D analogs like ED-71 and ED-120,[31e] the Posner group reported the preparation of 2-fluoroalkyl



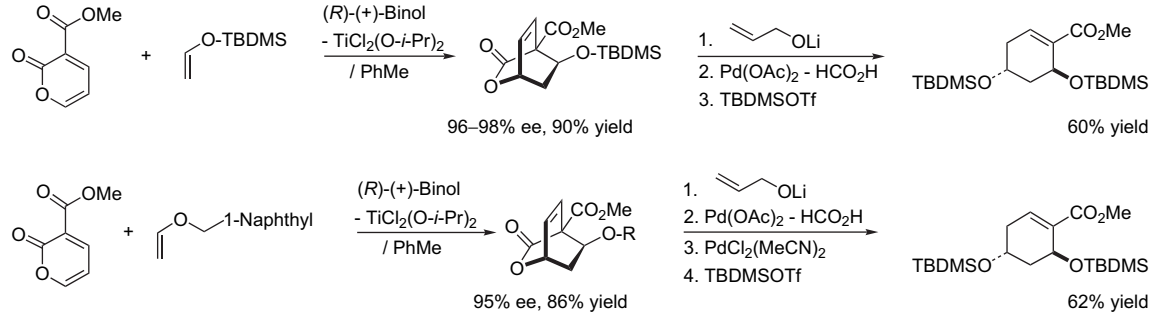
Scheme 125.



Scheme 126.



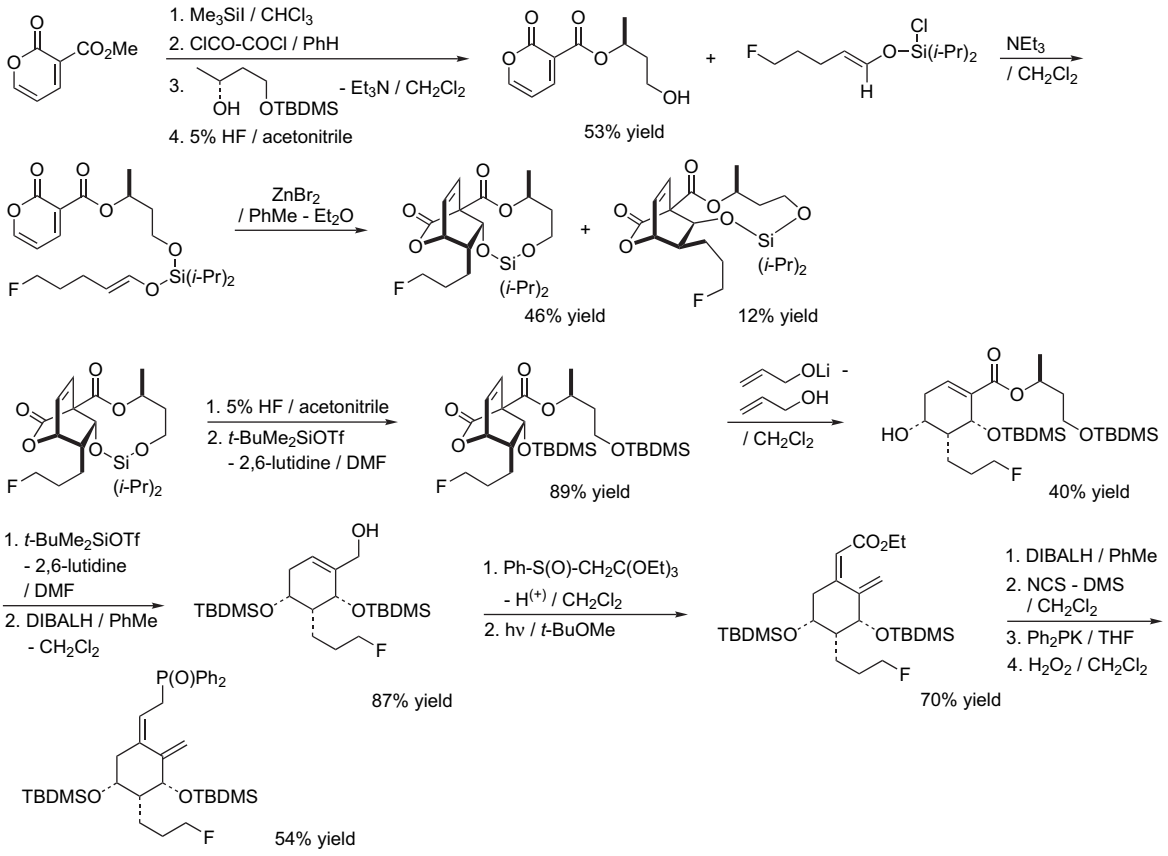
Scheme 127.



Scheme 128.

A-ring analogs of 1α,25-dihydroxyvitamin D_3 via a stereocontrolled Lewis acid-promoted intramolecular [4+2] cycloaddition of the (*S*)-pyrone fluorovinyl silaketal elaborated from the enantiomeric chiral auxiliary (*R*)-1,3-butanediol. The successive opening of the silaketal ring and the bicyclic lactone with spontaneous decarboxylation and concomitant conjugation of the double bond gave the tetrasubstituted cyclohexene. A two-carbon homologation of the intermediate allylic alcohol was performed through a Claisen rearrangement of the sulfinated orthoester followed by thermal sulfoxide extrusion and photochemical isomerization of *E* to *Z*-dienoate. Established reactions afforded the enantiopure phosphine oxide A-ring synthon. A fluorinated vitamin D analog was then reached from a Lythgoe-type coupling with the (+)-CD-ring ketone (Scheme 129).[181]

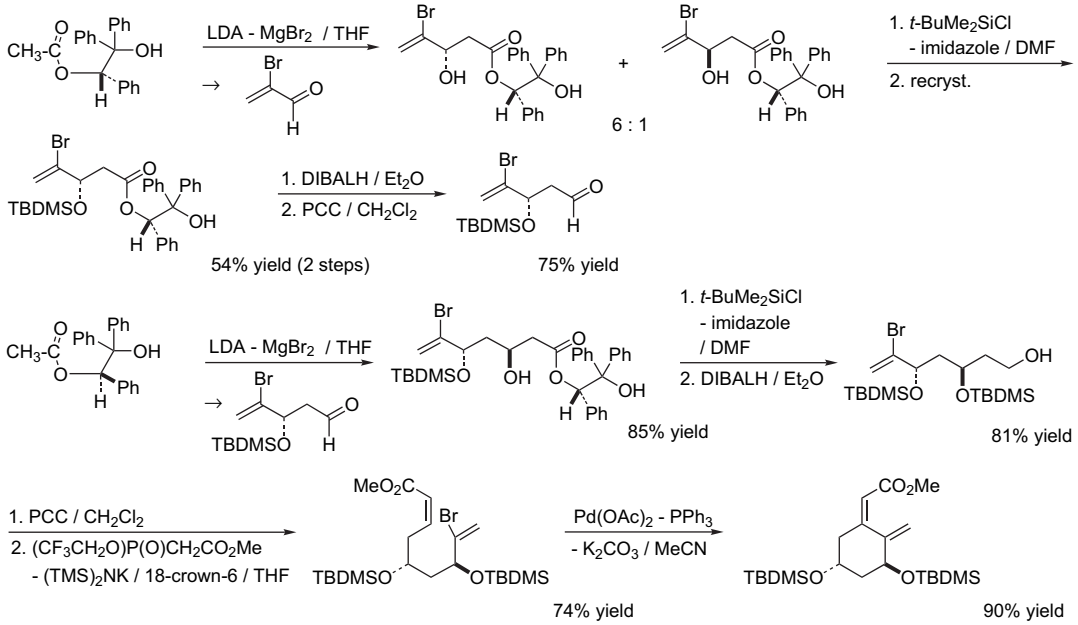
An elegant chiral synthesis of the A-ring synthon of 1α,25-dihydroxyvitamin D was described by Shimizu and coworkers and involved the formation of the two stereogenic centers C(1) and C(3) by two successive asymmetric Braun aldol reactions of each enantiomer of the 1,2,2-triphenylethan-1,2-diol-derived chiral acetate with α-bromoacrolein. At this stage, the stereoselective conversion of the acyclic adduct, 8-bromo-2,8-nonadienoate, into the exocyclic diene system was realized by a palladium-catalyzed intramolecular Heck reaction. It should be mentioned that, during the



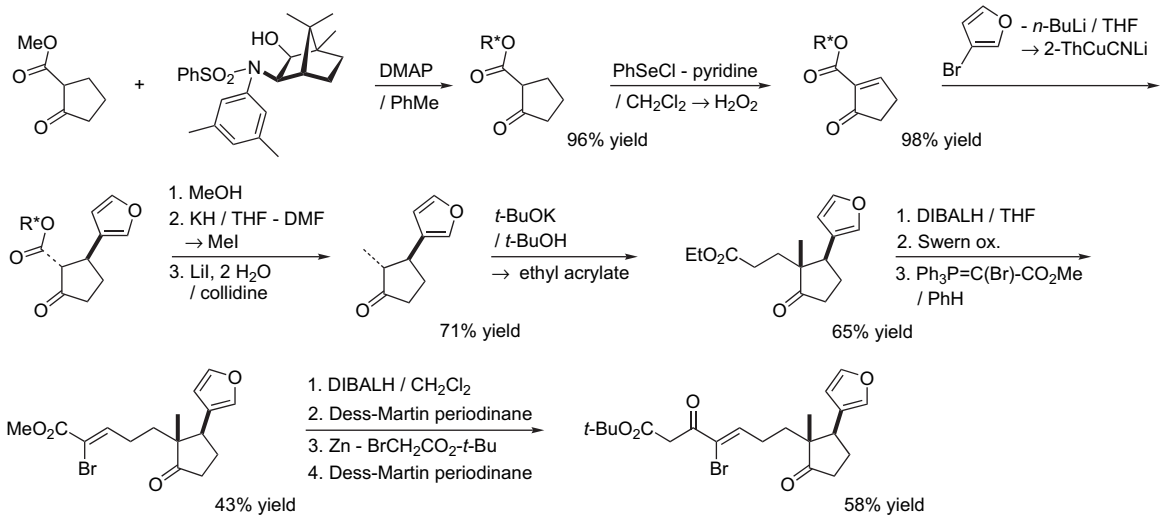
Scheme 129.

cyclization step, the (*E*) double bond changed to a (*Z*) configuration, as desired (Scheme 130).[182]

A range of toxic steroids, named cardenolides, were considered as interesting cardiotonic agents. In 2002, Deslongchamps and co-workers reported the synthesis of their tetracyclic skeleton possessing unusual hydroxylated cis AB- and CD-ring junctions by anionic polycyclization. The synthetic approach started with the elaboration of an enantiopure brominated Nazarov reagent obtained by the diastereoselective addition of a higher-order cuprate derived from 3-bromofuran to the α,β-unsaturated β-keto ester of a borneol chiral auxiliary (Scheme 131). A double Michael cycloaddition between the previous Nazarov reagent and



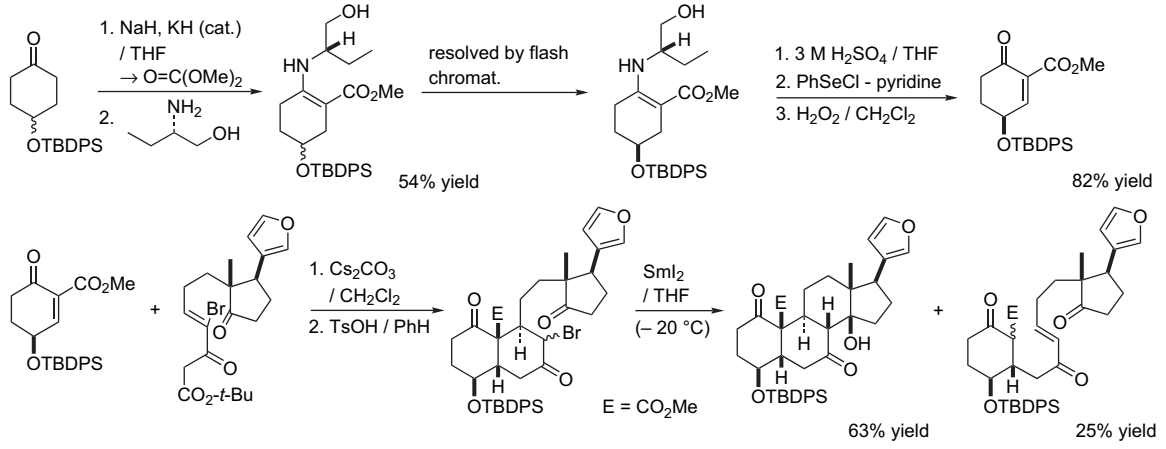
Scheme 130.



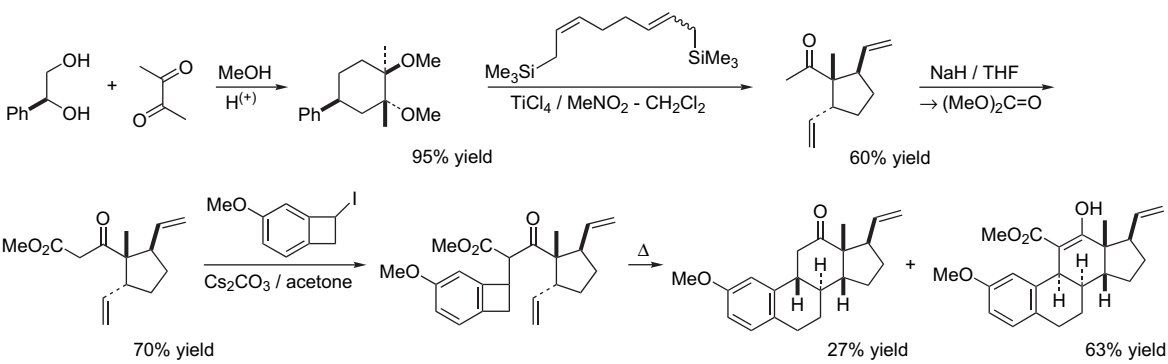
Scheme 131.

a chiral cyclohexenone, obtained by desymmetrization of 4-silanoxycyclohexanone and resolved by flash chromatography, allowed the construction of the cis-fused AB-ring unit. Then, reduction of the bromide with samarium(II) iodide and aldolization with the cyclopentanone produced the tetracyclic product (Scheme 132).[183]

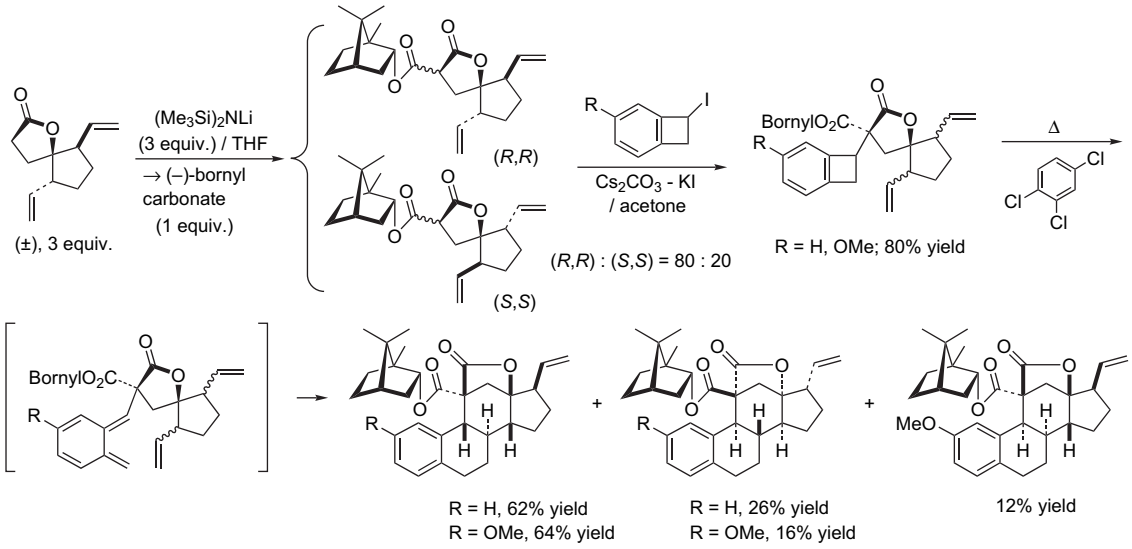
As shown by Santelli and co-workers, diallylation of 1,2-diacetals derived from 2,3-butanedione by 1,8-bis-(trimethylsilyl)-octa-2,6-diene (BISTRO) followed by a pinacol-type rearrangement generated 1-acetyl-1-methyl-2,5-divinylcyclopentanes as a mixture of *meso*- and DL-isomers. The use of a mixed ketal obtained from methanol and (+)-1-phenyl-1,2-ethanediol gave access to the non-racemic DL-building block, which was readily engaged in a synthesis of unnatural 12-oxosteroids involving intramolecular *o*-quinodimethane cycloaddition as a key step. The steroid precursor was formed by alkylation of a β-keto ester



Scheme 132.



Scheme 133.



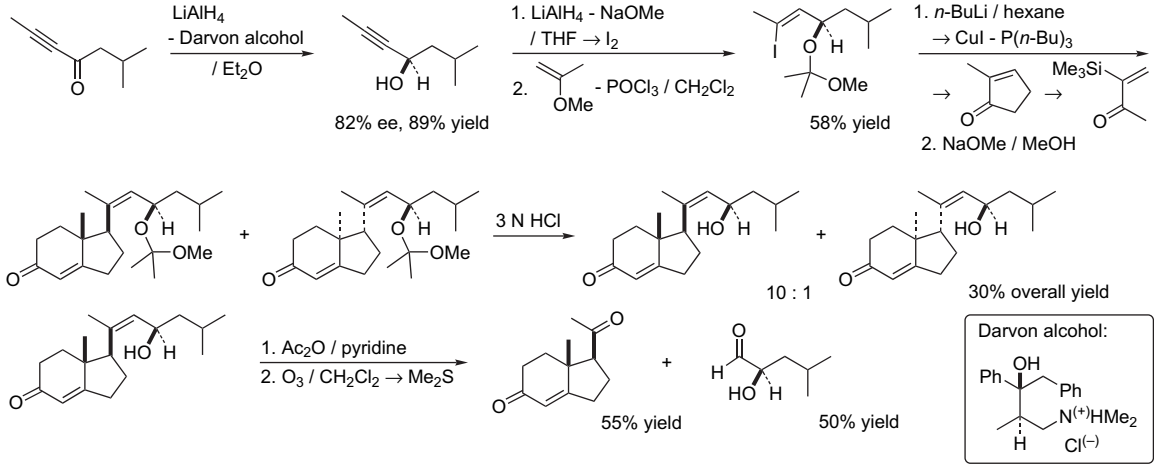
Scheme 134.

enolate with a racemic iodobenzocyclobutene, as outlined in Scheme 133. Both cycloadducts exhibited a cis CD-ring junction and the BC cis-fused major isomer resulted from an *endo* transition state.[184] In a recent paper, this research group also reported that the addition of BISTRO to succinic anhydride afforded a racemic DL-spirolactone, the acylation of which with (−)-bornyl carbonate operated a kinetic resolution and yielded the two expected lactones with diastereoselectivities up to 80:20. These compounds served as precursors to non-racemic C-11 functionalized estrane derivatives such as 11α-alkoxycarbonyl-11β,13β-(γ-carbolactone)-17β-vinylgonatri-1,3,5(10)-enes (Scheme 134).[185]

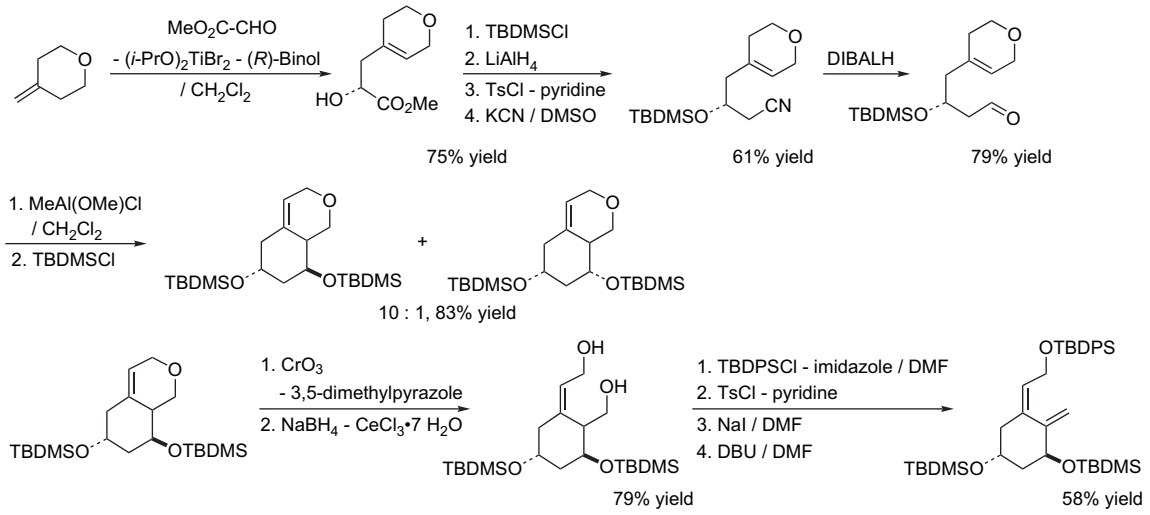
4.2. Use of chiral metal–ligand complexes

Some representative methods involving chiral metal organic ligand catalysts have been reported to elaborate different steroid building blocks. In 1984, Takahashi and co-workers proposed the use of lithium aluminum hydride in the presence of Darvon alcohol for the asymmetric reduction of a propargylic ketone. The resulting optically pure alcohol was modified to (*R*)-vinyl iodide and used in the preparation of (+)-(1*R*)-acetyl-(7a*R*)-methyl-4-hydroinden-5-one, a chiral steroid CD-ring synthon. The key steps were the enantioselective Michael addition of an alkenylcopper/phosphine complex, derived from the (*R*)-vinyl iodide, to 2-methyl-2-cyclopentenone and the subsequent conjugate addition of the resultant enolate to 3-trimethylsilylbutenone (Scheme 135).[186]

In 1992, the Hoffmann-La Roche group reported an asymmetric synthesis of a key 1α,25-dihydroxyvitamin D_3 A-ring synthon, which utilized a highly stereoselective intramolecular carbonyl-ene reaction to set up the proper configuration of the hydroxyl group at C(1) and the (*Z*)-double bond. The requisite hydroxylated δ,ε-unsaturated aldehyde was elaborated from a Mikami asymmetric *ene* reaction of methyl glyoxylate with 4-methylene-tetrahydropyran and cyclized in the presence of methoxymethylaluminum chloride to give a 10:1 mixture of isomeric alcohols. Allylic oxidation of the dihydropyran ring provided the lactone intermediate, which was degraded to form the desired allylic alcohol (Scheme 136).[187] Later, a sequence of regioselective



Scheme 135.



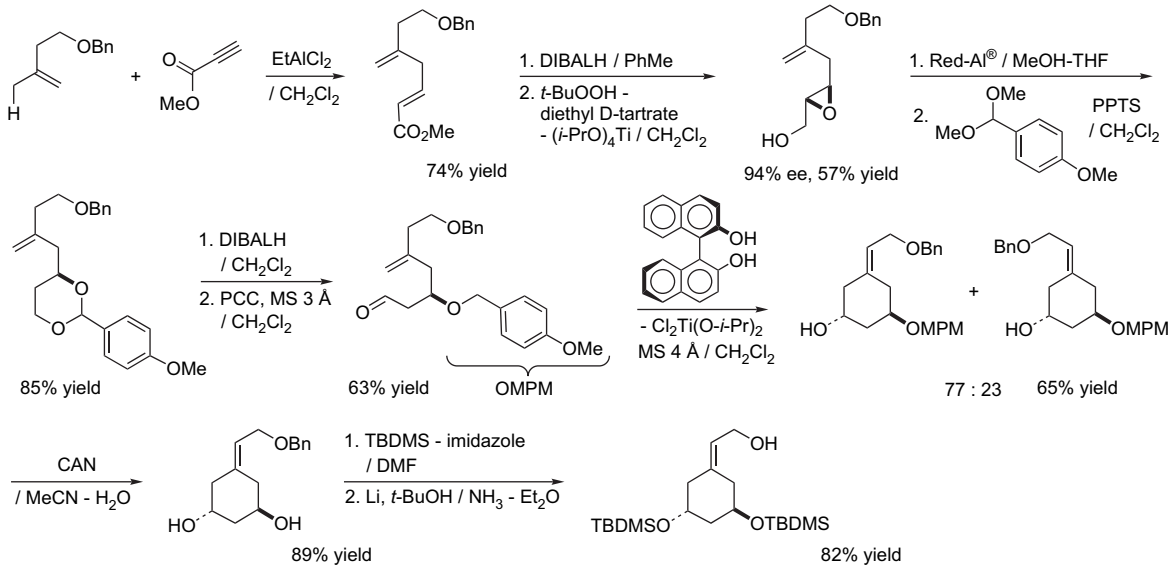
Scheme 136.

propiolate-ene reaction of a homoallylic alcohol followed by catalytic enantioselective Sharpless epoxidation of the resulting allylic alcohol and catalytic enantioselective carbonyl-ene cyclization was proposed by Mikami to prepare the A-ring of the 19-nor-22-oxa and 2-methyl-19-nor-22-oxa vitamin D_3 analogs (Scheme 137).[188,189]

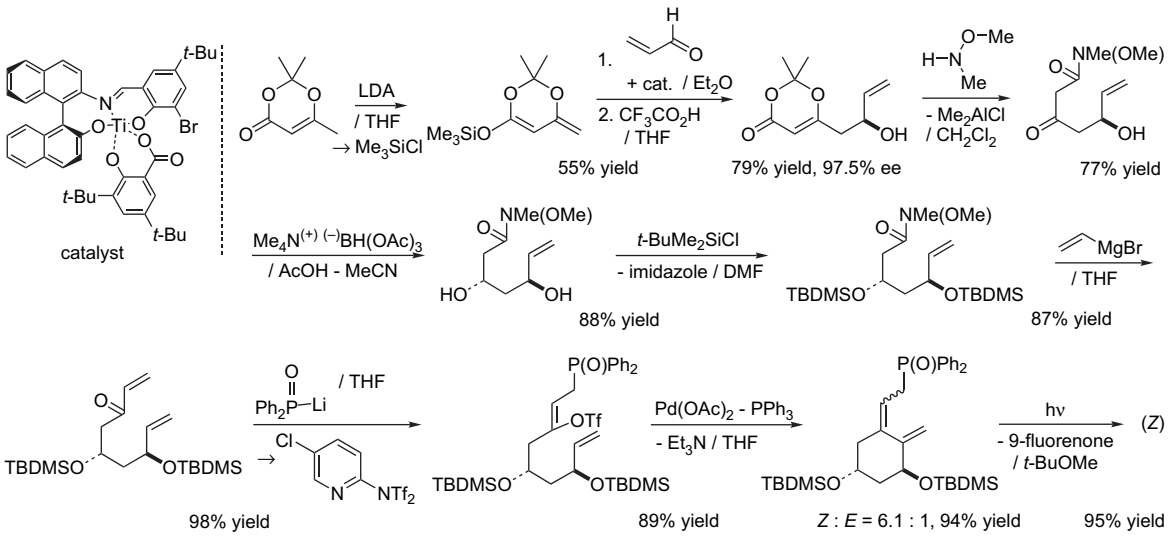
Hatakeyama developed an efficient alternative synthesis of the A-ring allylic phosphine oxide in nine steps and 23% overall yield from the commercially available 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one. The first aldol reaction between a cyclic ketene acetal and acrolein catalyzed by Carreira's chiral titanium(IV) complex[190] was carried out according to Vandewalle's work[191] and led to the corresponding allylic alcohol with a high 97% ee, a useful intermediate from which Vandewalle had already prepared the enyne building block required in the Trost approach. The conjugate addition of lithium diphenylphosphine oxide to a vinyl ketone derivative and triflation of the formed enolate allowed the stereoselective construction of the enol triflate, which underwent a palladium-catalyzed Heck-type cyclization. Photochemical isomerization of the product to the (*Z*)-isomer furnished the A-ring synthon (Scheme 138).[191] Moreover, the enyne building block required in the Trost approach was prepared by Vandewalle starting from a similar enantiomerically enriched allylic alcohol (Scheme 139).[192]

Mouriño and co-workers synthesized the 3-deoxy-2,25-dihydroxyvitamin D analog starting from an optically active enynol. The enantioselective approach to the A-ring synthon involved a catalytic asymmetric Keck allylation and an intramolecular Heck cyclization of a (*Z*)-vinyl iodide as the key steps. A high enantiomeric excess (97%) was obtained when the allylation reaction was carried out at 0 °C with allyltributylstannane and 10% of the catalyst (*R*)-Binol/Ti(O-*i*-Pr)$_4$ 2:1 (Scheme 140).[193]

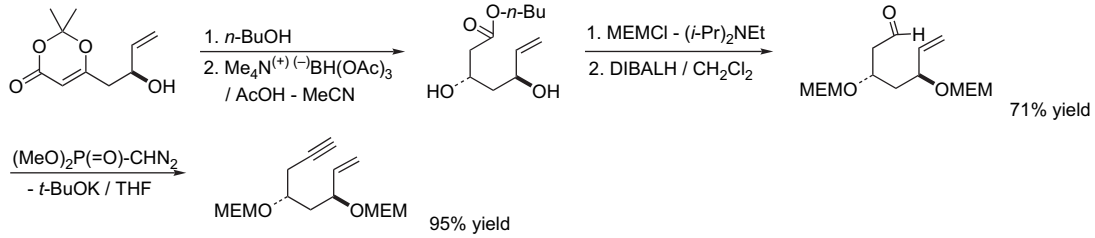
A furan approach to the synthesis of the A-ring of vitamin D analogs was proposed by Miles and Connell. In this work, the known furanyl ketone precursor was reduced using



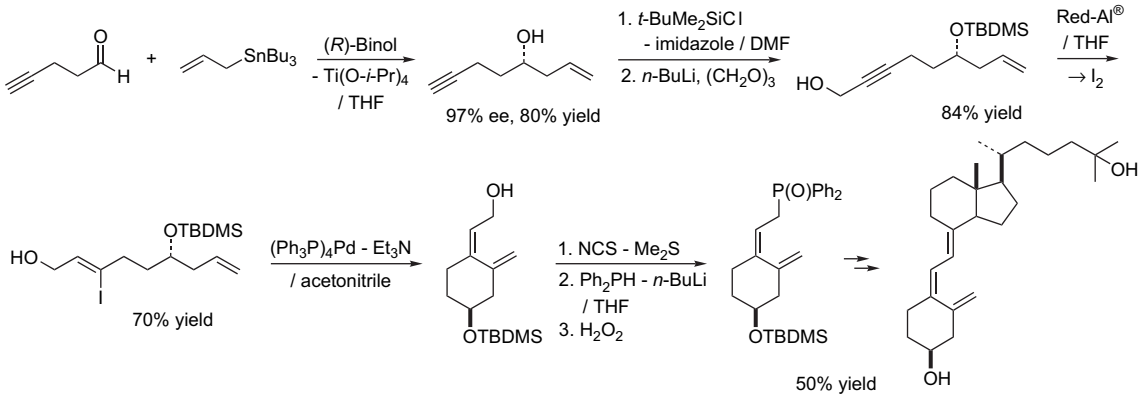
Scheme 137.



Scheme 138.



Scheme 139.

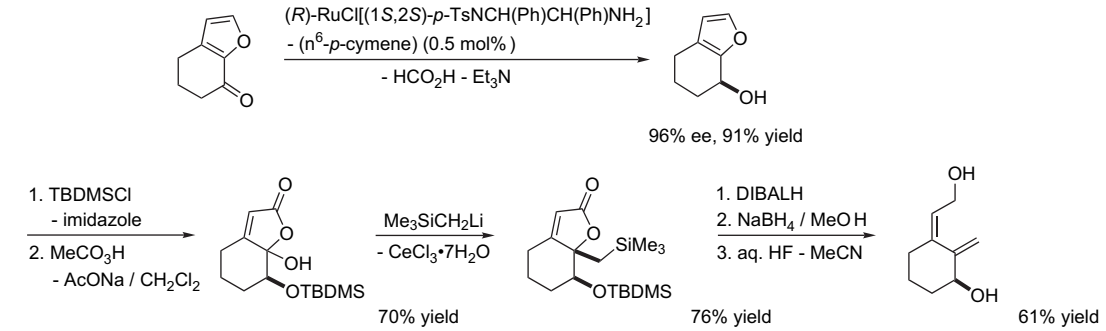


Scheme 140.

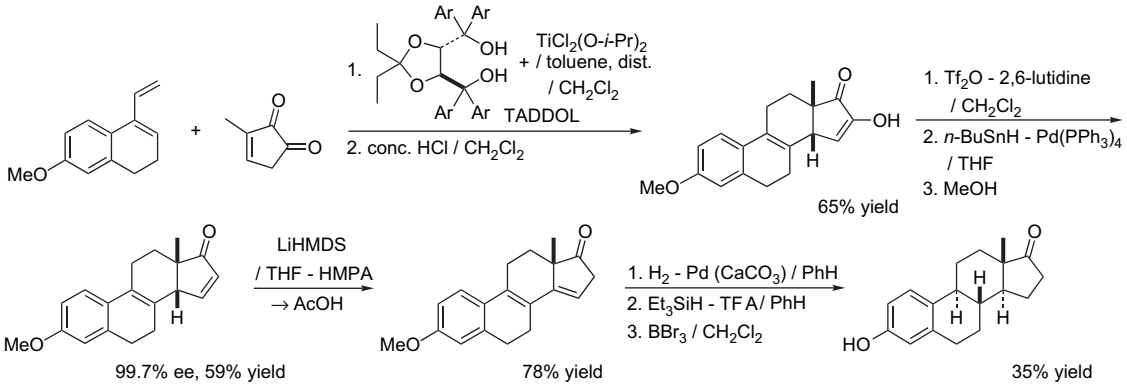
Noyori's ruthenium(II) asymmetric transfer hydrogenation to give the corresponding alcohol in 96% ee. Oxidation of the silyl-protected derivative by peracetic acid buffered with NaOAc generated the γ-hydroxybutenolide. A three-step strategy based on the Peterson olefination was developed to complete the preparation of the desired (*Z*)-dienol (Scheme 141).[194]

Quinkert and co-workers established the use of Dane's diene by carrying out a chiral Lewis acid-catalyzed Diels–Alder reaction with 3-methyl-cyclopent-3-ene-1,2-dione. In the presence of $TiCl_2(O\text{-}i\text{-}Pr)_2$ as Lewis acid modified by the optically active Seebach TADDOL ligand, the expected *cis*-hydrindane cycloadduct was isolated in 65% yield and 93% ee.[195] Base-promoted isomerization of the 2-cyclopentenone steroid D-ring to 3-cyclopentenone followed by catalytic hydrogenation of the styrene moiety generated the trans-fused bicyclic system. Ionic hydrogenation using Et_3SiH/CF_3CO_2H and BBr_3 ether deprotection furnished (+)-estrone with 99.7% ee (Scheme 142).[196]

A new oxazaborolidinium cationic catalyst, recently developed by Corey, was found to be an efficient chiral Lewis acid for asymmetric [4+2]-cycloaddition between Dane's



Scheme 141.

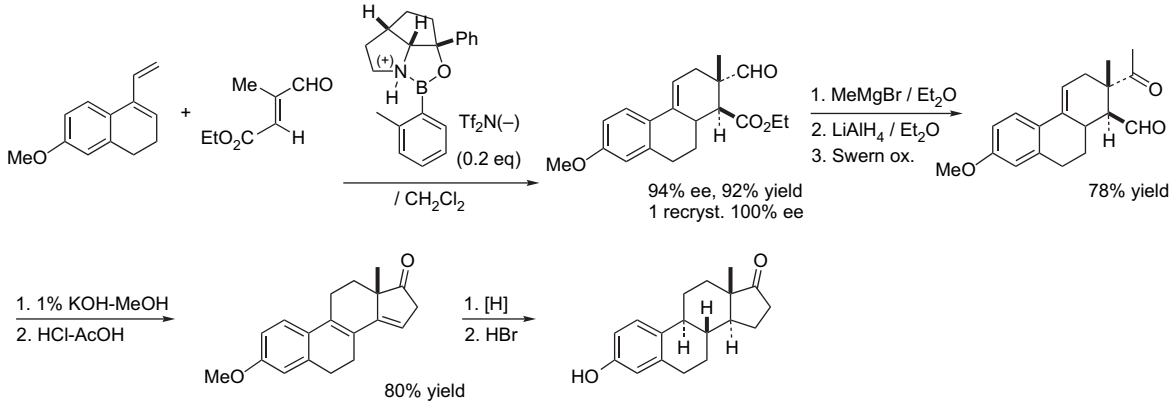


Scheme 142.

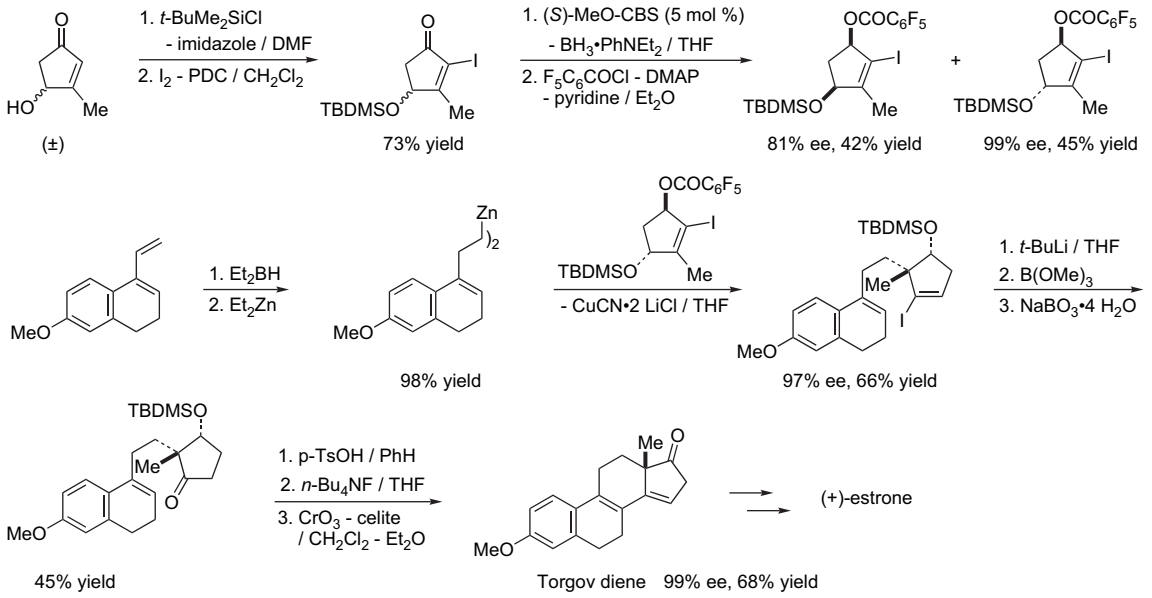
diene and α,β-unsaturated ester aldehydes. As shown in Scheme 143, the Diels–Alder reaction proceeded with high enantioselectivity (94% for *endo*) and the resulting cycloadduct was readily converted into (+)-estrone by aldol cyclocondensation and stereoselective reduction of the C(14)–C(15) and C(8)–C(9) double bonds of the tetracyclic dienone intermediate. An access to the important third-generation oral contraceptive, desogestrel, was also proposed.[197]

A tandem asymmetric allylic substitution/Heck ring-closure reaction was employed by Soorukram and Knochel for the construction of the enantiomerically enriched Torgov diene, a suitable precursor of (+)-estrone. The chirality was introduced via a CBS reduction of the iodo derivative of 4-hydroxy-3-methyl-2-cyclopent-2-en-1-one and the quaternary carbon center was elaborated by using a Cu(I)-mediated anti-S_N2' substitution (Scheme 144).[198]

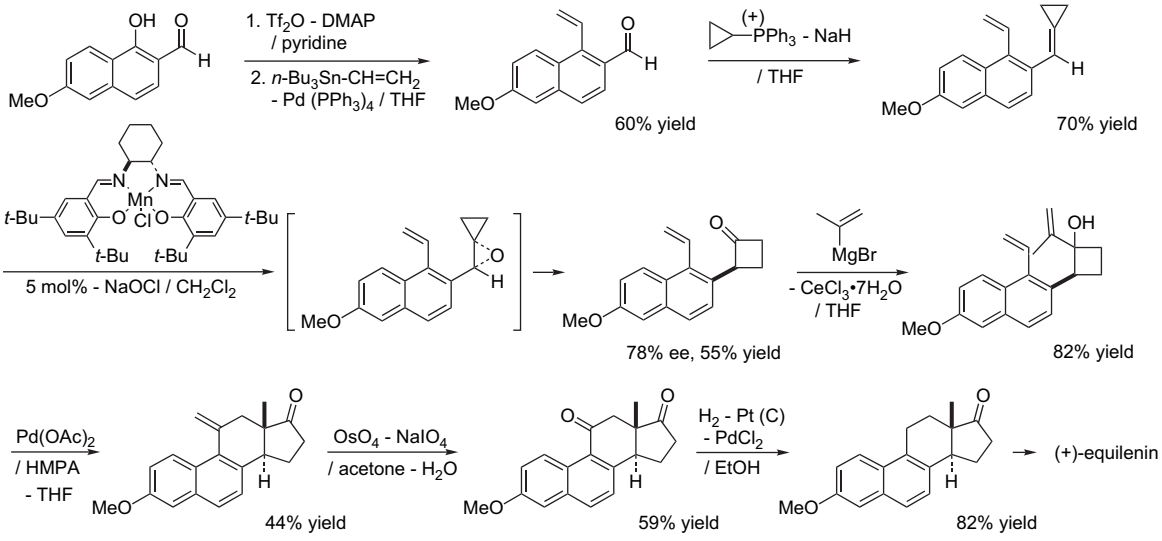
Nemoto and Ihara proposed a different strategy for the enantioselective synthesis of the natural (+)-equilenin, based on two cascade ring-expansion reactions, which constituted the key steps of this approach. The first reaction was reported as a chiral (*R*,*R*)-(salen)Mn(III) complex-catalyzed asymmetric epoxidation of cyclopropylidene and its enantiospecific rearrangement, and the second as a palladium(II)-mediated cascade reaction of the vinylcyclobutanol, including ring expansion-insertion steps (Scheme 145).[199]



Scheme 143.



Scheme 144.



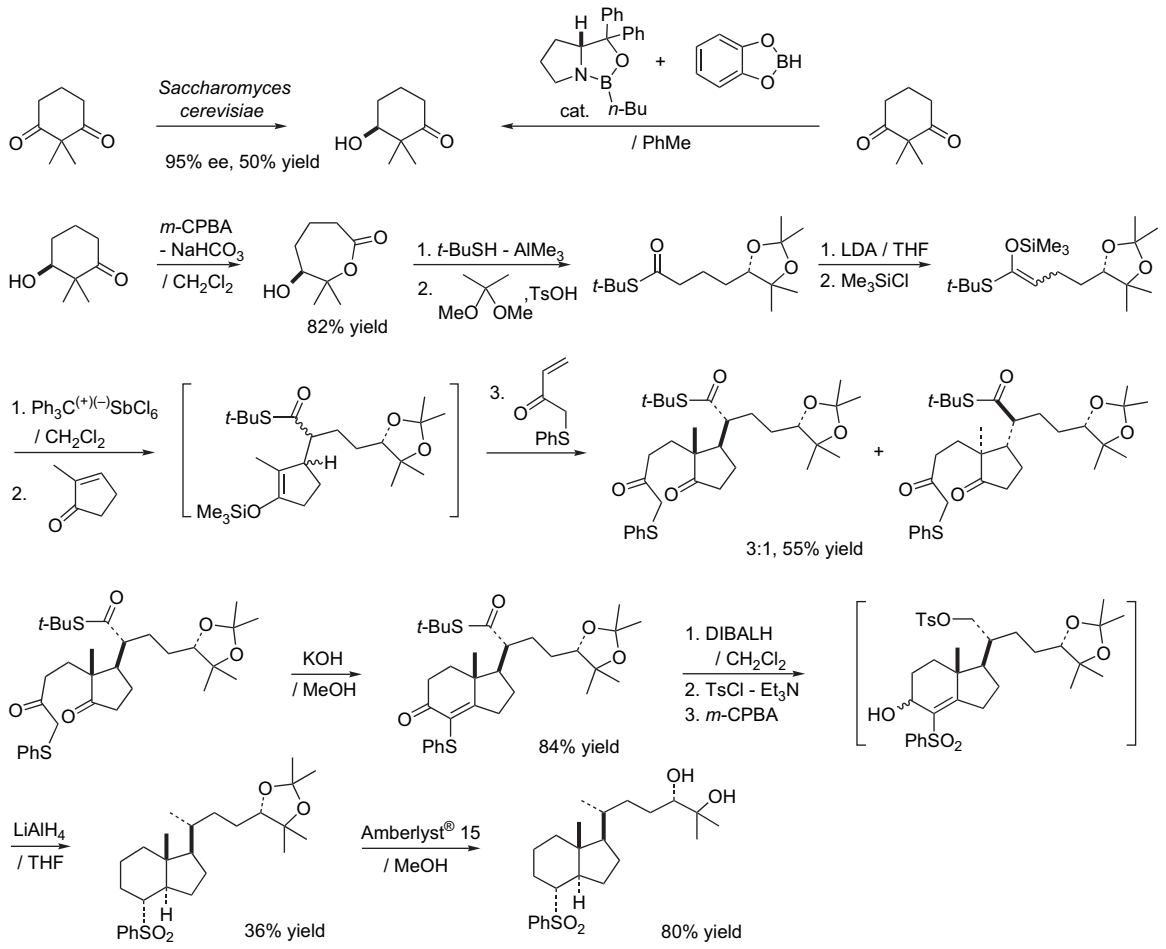
Scheme 145.

Wicha reported the preparation of an optically pure CD-ring side chain fragment of 24,25-dihydroxyvitamin D_3 by using a tandem Mukaiyama–Michael conjugate addition of a chiral ketene acetal with 2-methylcyclopent-2-en-1-one and thiophenylmethyl vinyl ketone. The required ketene acetal was accessible by the reduction of 2,2-dimethylcyclohexan-1,3-dione by baker's yeast or the appropriate oxazaborolidine/borane complex reagent. The stereochemistry of the first addition was consistent with a *like* attack on the cyclopentenone system, the facial selectivity of which was influenced by the C(24) stereogenic center. The second addition delivered the Nazarov-type reagent exclusively *anti* to the C(17) center. After annulation, a remarkable double-hydride reduction of the C(21) tosylate and the 3β-hydroxy vinylsulfone led to the trans-fused bicyclic system (Scheme 146).[200,201]

Asymmetric hydrogenation of a β-diketone such as 1,5-dichloropentane-2,4-dione in the presence of a cheap ruthenium–optically active phosphine complex catalyst led to the C_2-symmetric (2*S*,4*S*)-1,5-dichloropentane-2,4-diol, which could be transformed into the corresponding (2*S*,4*S*)-diepoxypentane. This latter alkane was used by Vandewalle as a starting material for short alternative syntheses of A-ring precursors for the hormonally active 1α,25-dihydroxyvitamin D_3 and the 19-nor-analogs (Schemes 147 and 148).[191,202]

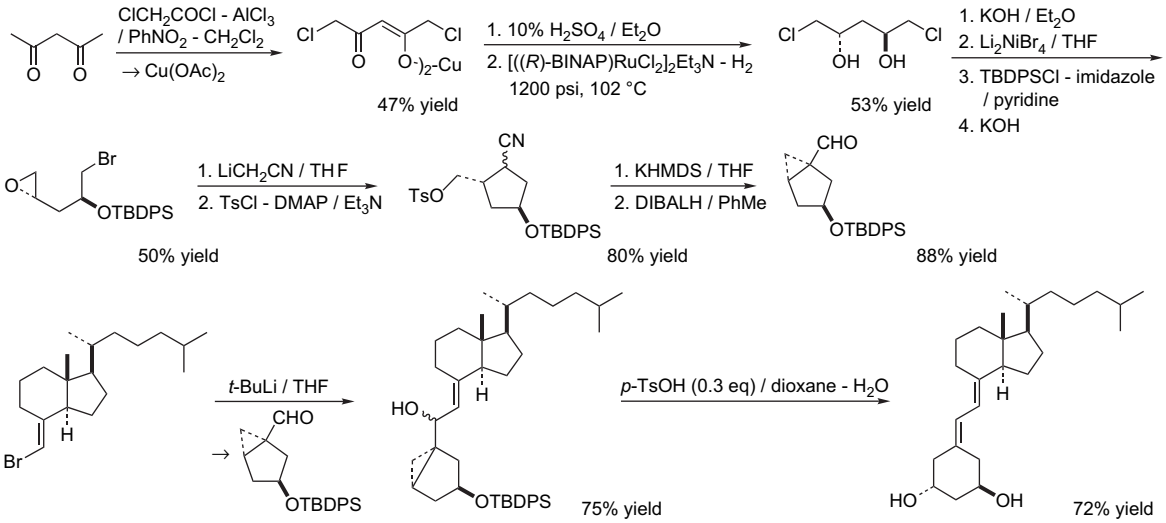
4.3. Use of chiral bases

A chiral lithium amide base-desymmetrization of 4-(*tert*-butyldimethylsiloxy) cyclohexanone allowed Parker and Dermatakis to prepare the corresponding (−)-*trans*-

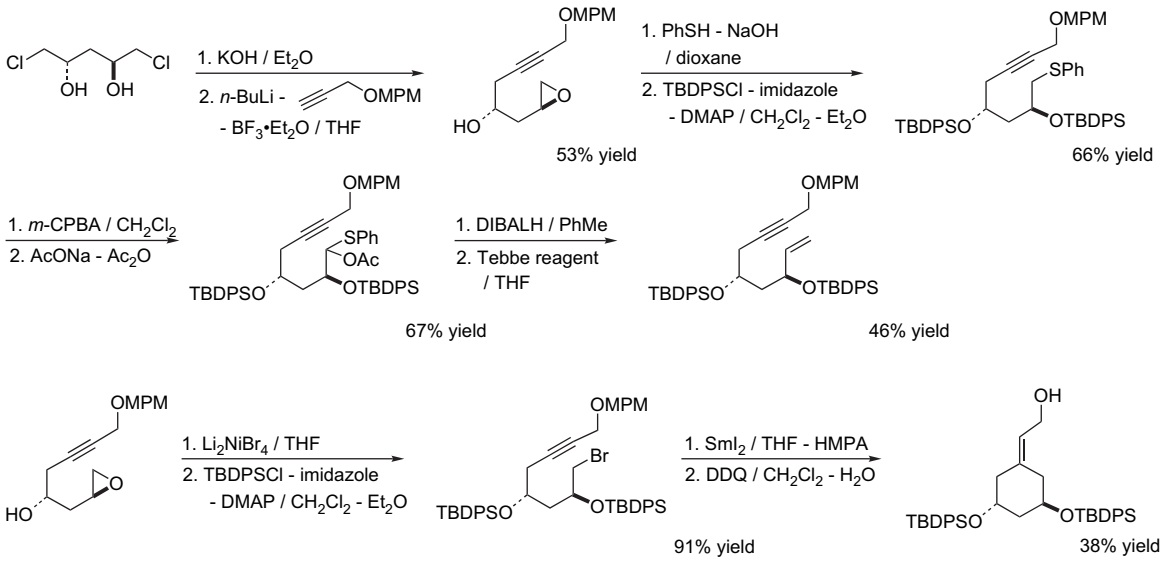


Scheme 146.

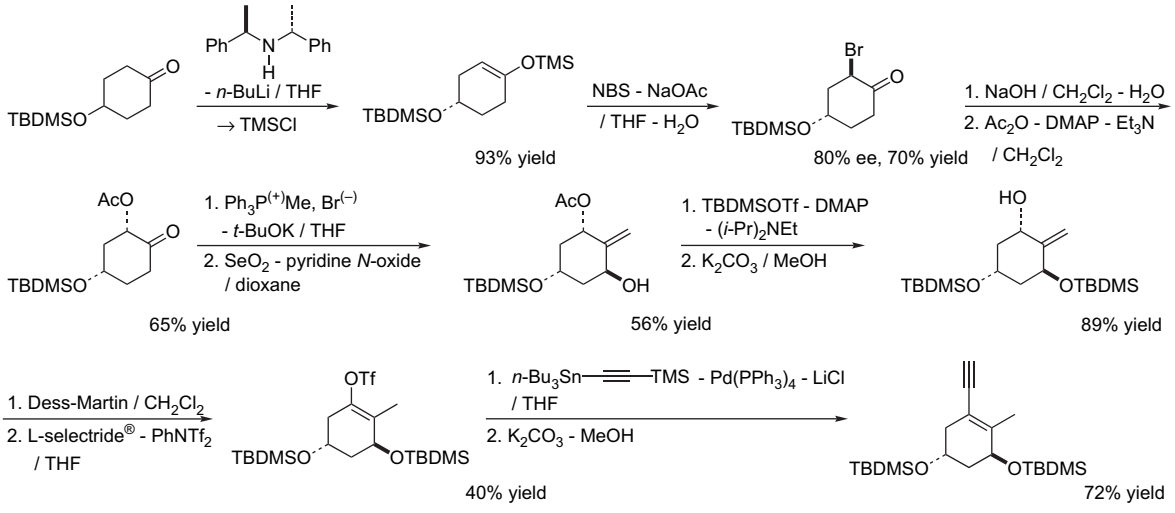
bromoketone, which was transformed in a few steps into the target enyne A-ring synthon of 1α-hydroxyvitamin D (Scheme 149).[203] Taking advantage of this enantioselective desymmetrization reaction, Gouverneur prepared the 1α-fluoro A-ring dienol, a known key intermediate for the synthesis of 1α-fluoro vitamin D_3 analogs. The novel key features of this approach included a palladium-mediated C–C coupling for the preparation of an advanced dienylsilane intermediate and a substrate-controlled diastereoselective electrophilic fluorodesilylation (Scheme 150).[204]



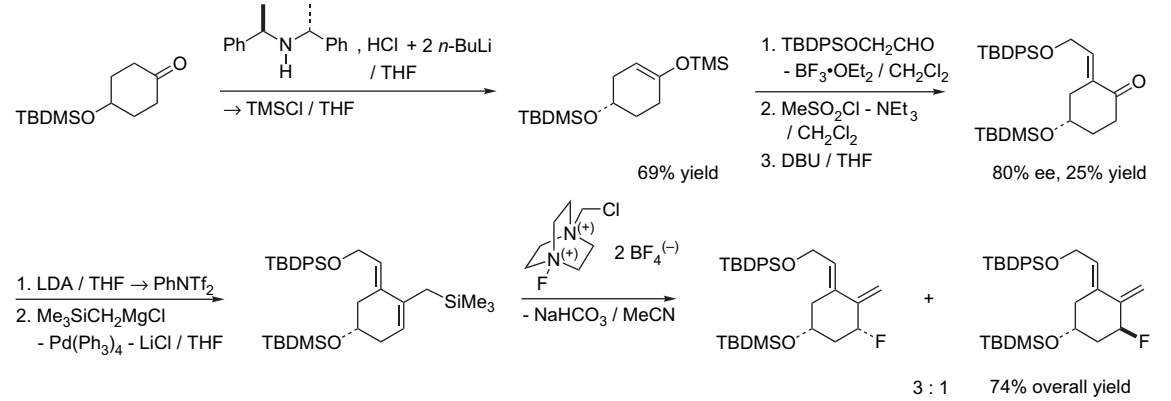
Scheme 147.



Scheme 148.



Scheme 149.



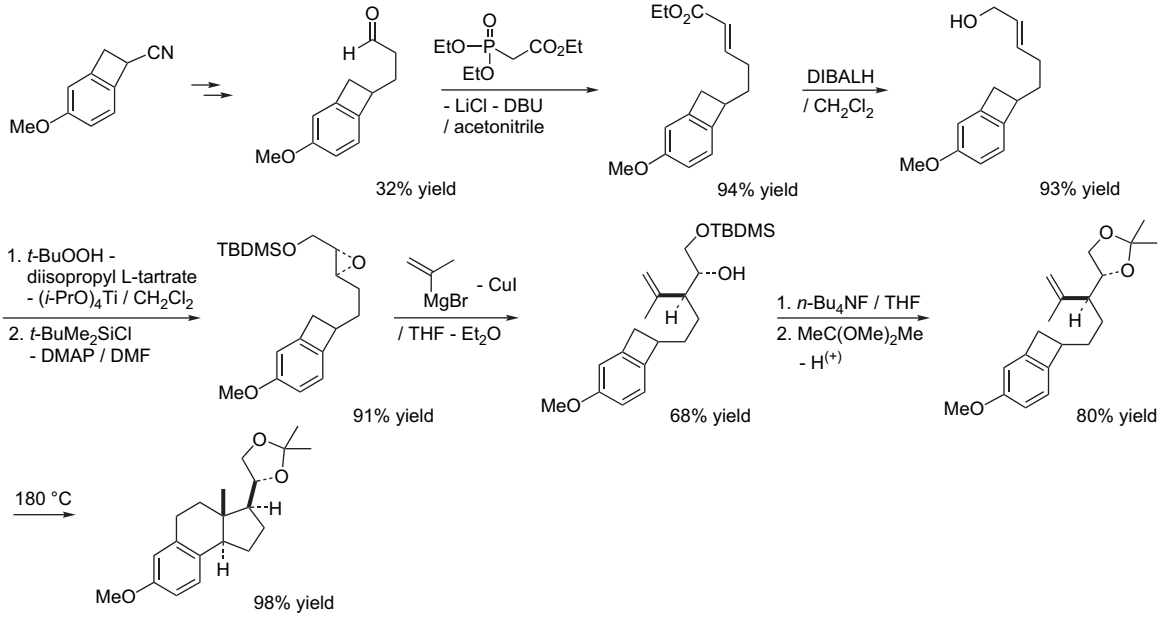
Scheme 150.

5. Sharpless epoxidation of allylic alcohols and dihydroxylation of olefins

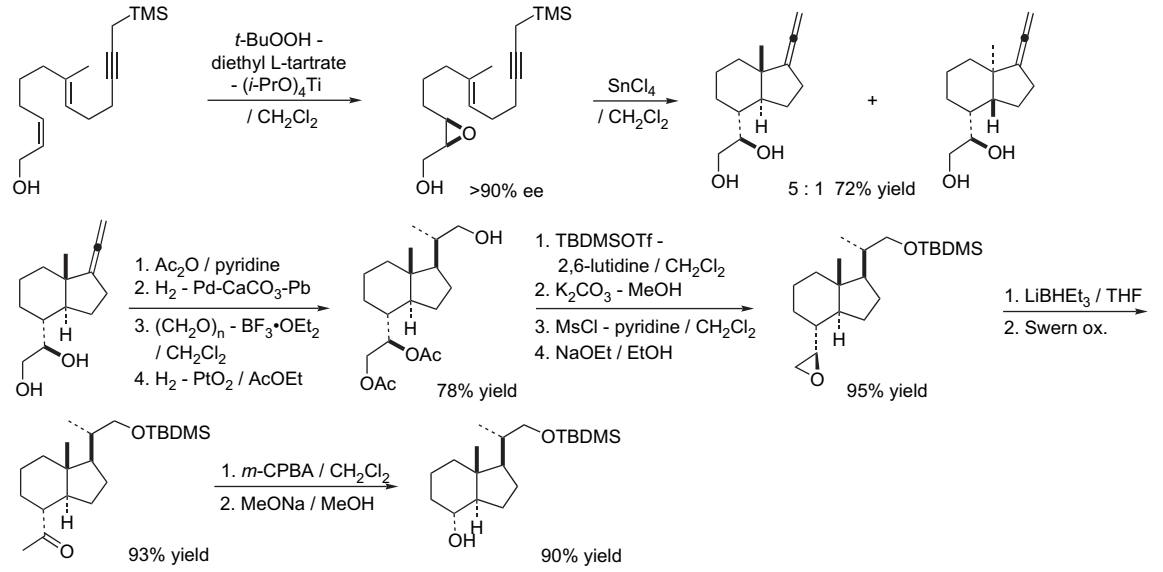
Formation of the enantiomerically active des-AB trienic steroid was realized by thermolysis of an optically pure alkenic benzocyclobutene. From 1-cyano-4-methoxybenzocyclobutene, Nemoto and Fukumoto prepared the *trans* primary allyl alcohol, which was enantioselectively epoxidized according to Sharpless methodology. Introduction of the dienophile moiety was performed by regio- and stereoselective epoxide ring opening involving nucleophilic addition of the isoprenyl Grignard in the presence of copper(I) salts. Thermal cyclization of the acetonide gave the trans-fused adduct in 98% yield (Scheme 151).[205]

A stereoselective epoxy alcohol-initiated cationic polyalkene cyclization, prompted by Johnson's biomimetic approach, was developed by Takano and co-workers and exploited for the synthesis of the Inhoffen–Lythgoe diol. The starting epoxy alcohol was accessible from the corresponding acyclic allylic alcohol by Sharpless asymmetric epoxidation and the intramolecular nucleophilic opening of the epoxide took place upon treatment with $SnCl_4$ to give the bicyclic allene diol with a trans-junction. Cyclization of the (*Z*)-epoxy alcohol showed a higher diastereoselectivity, compared with the corresponding (*E*)-isomer. Functional-group manipulations generated the expected hydrindanol (Scheme 152).[206]

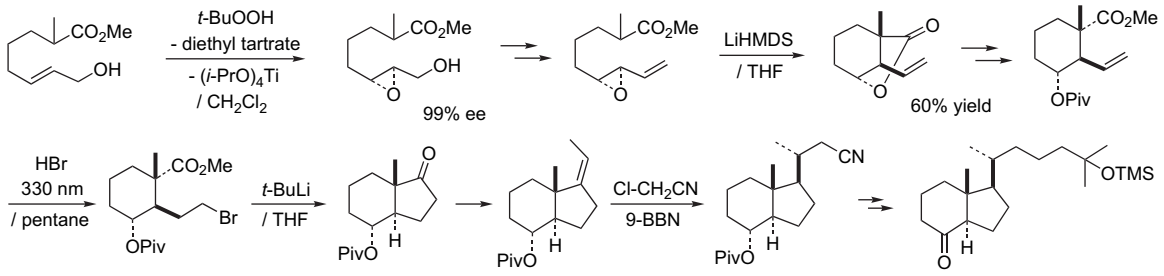
Stork and co-workers performed a stereoselective allylic epoxide cyclization to a lactone derivative for the construction of a CD-*trans* indanone system. For the formation of the optically pure lactone, it was necessary to start with the enantiopure allylic epoxide made by Sharpless epoxidation



Scheme 151.



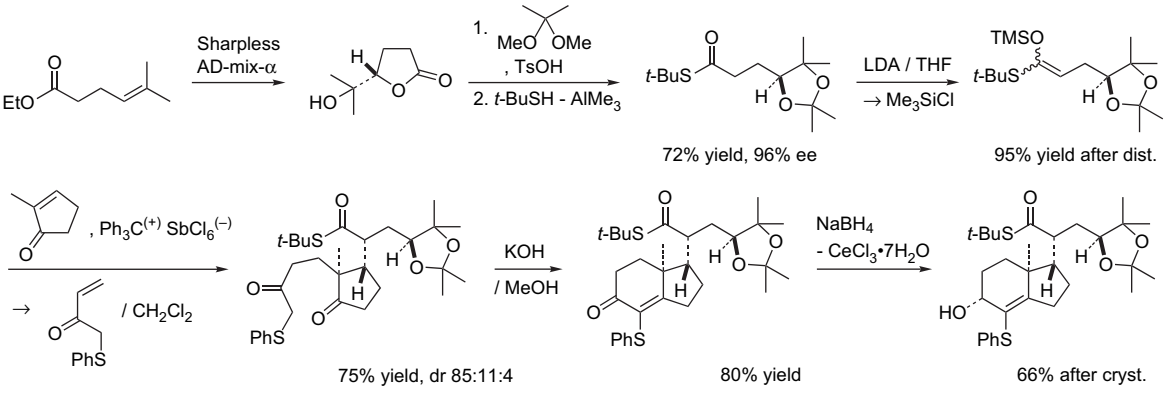
Scheme 152.



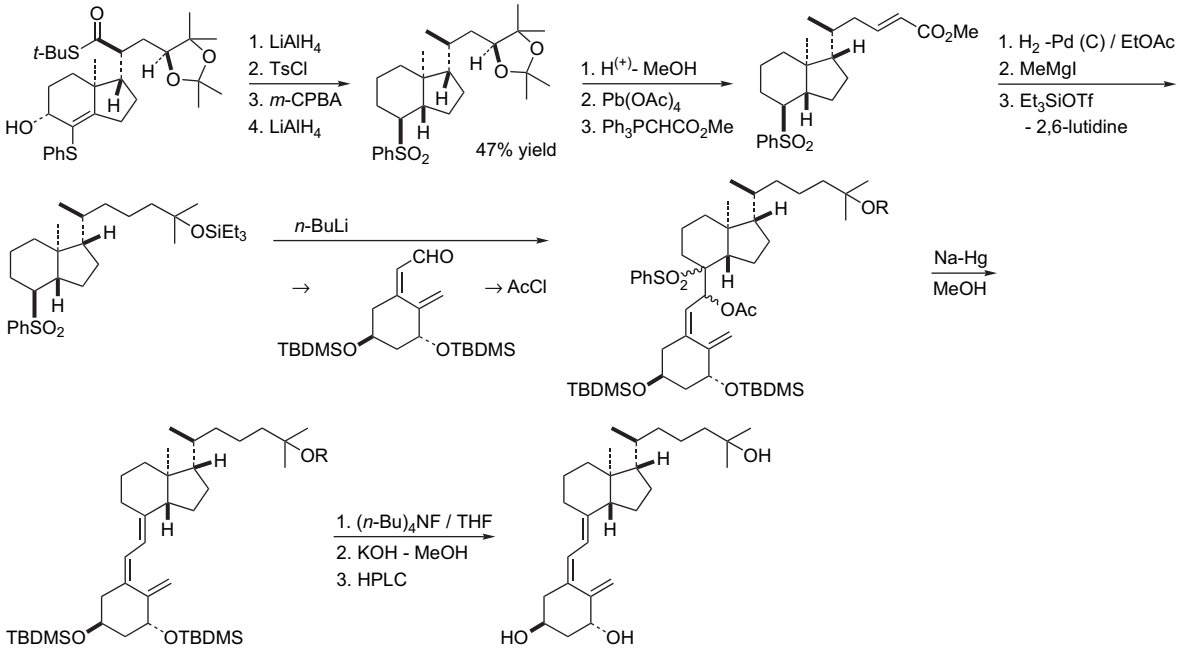
Scheme 153.

of the allylic alcohol, and to perform an intramolecular epoxide ring opening by the ester enolate. The completion of the 25-hydroxylated Windaus–Grundmann ketone from the bicyclic lactone is shown in Scheme 153. However, the synthetic sequence has not been reported in detail.[168a,207]

During his studies on *ent*-vitamin D synthesis and its analogs, Wicha realized the Sharpless asymmetric dihydroxylation of methyl 5-methyl-4-hexenoate with the commercially available AD-mix-α to give directly the hydroxy γ-lactone. Further transformations afforded the homochiral (*S*)-ketene acetal, which underwent a diastereoselective tandem Mukaiyama–Michael addition with 2-cyclopentenone and 1-(phenylthio)but-3-en-2-one followed by vinyl sulfone reduction, already reported in Section 4, as the key steps (Scheme 154). The *trans*-hydrindane sulfone and the A-ring aldehyde were then coupled according to Julia's olefination reaction (Scheme 155).[208] Unfortunately, the resulting 1α,25-dihydroxyvitamin D_3 enantiomer did not show any significant affinity to the vitamin D receptor.[209]



Scheme 154.



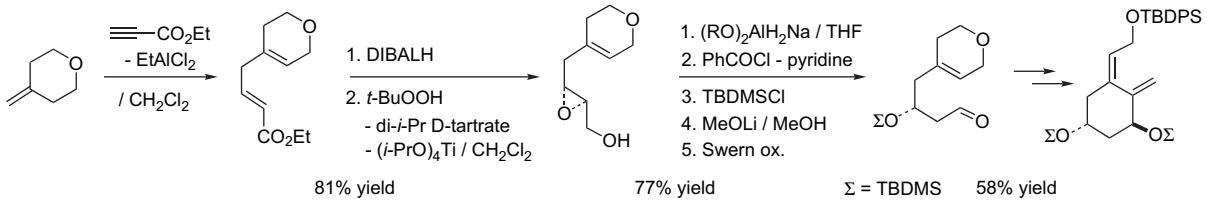
Scheme 155.

An alternative route to the δ,ε-unsaturated aldehyde, previously employed in the synthesis of the A-ring allylic alcohol and depicted in Scheme 136, was proposed by the same authors. Their approach relied on two key steps, including Sharpless asymmetric epoxidation of the allylic alcohol generated from the *ene* reaction of 4-methylene-tetrahydropyran with ethyl propiolate and hydroxyl-assisted regioselective epoxide reduction with sodium bis(2-methoxyethoxy)aluminum hydride, which sets up the 3β-hydroxyl function (Scheme 156).[188]

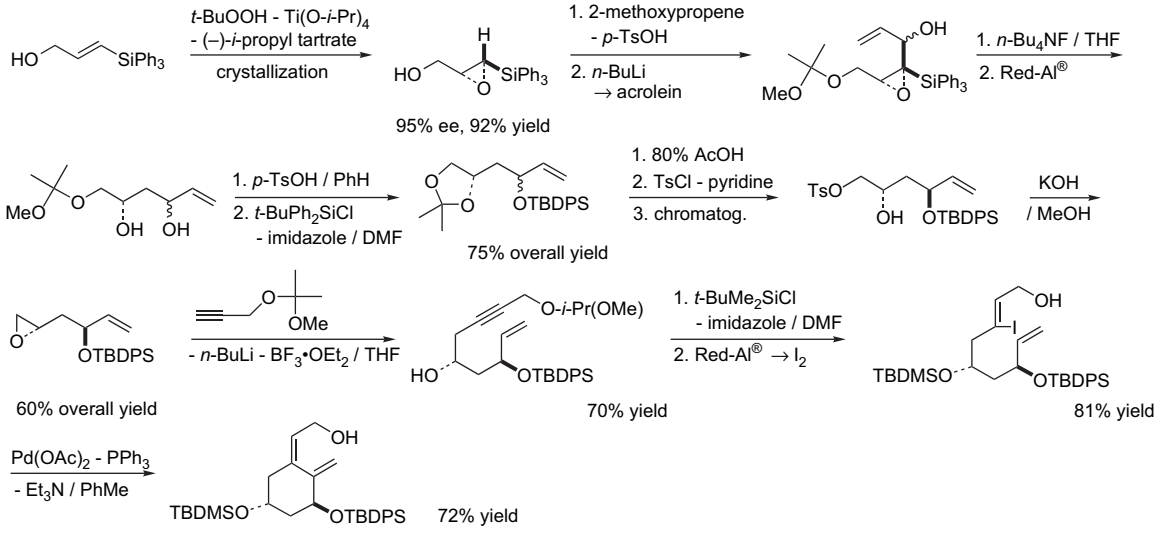
Later, Wicha and co-workers reported another synthesis of the A-ring dienol synthon that started from 3-triphenylsilylglycidol, a substrate easily obtained by Sharpless epoxidation of the corresponding allylic alcohol. Intramolecular Heck cyclization of the advanced iododiene intermediate led directly to the target compound (Scheme 157). A similar strategy was successfully applied to an acyclic precursor prepared from L-(+)-malic acid.[210]

In Shimizu's approach shown in Scheme 158, the key intermediate dienoate for the synthesis of the 1α-hydroxyvitamin D_3 A-ring was synthesized from (*E*)-8-bromo-2,8-nonadienoate using also a stereoselective palladium-catalyzed intramolecular cyclization. The acyclic compound was easily accessible via Sharpless epoxidation of an allylic alcohol and reductive cleavage of the alkenyloxirane that established the absolute stereochemistry at C(3).[182]

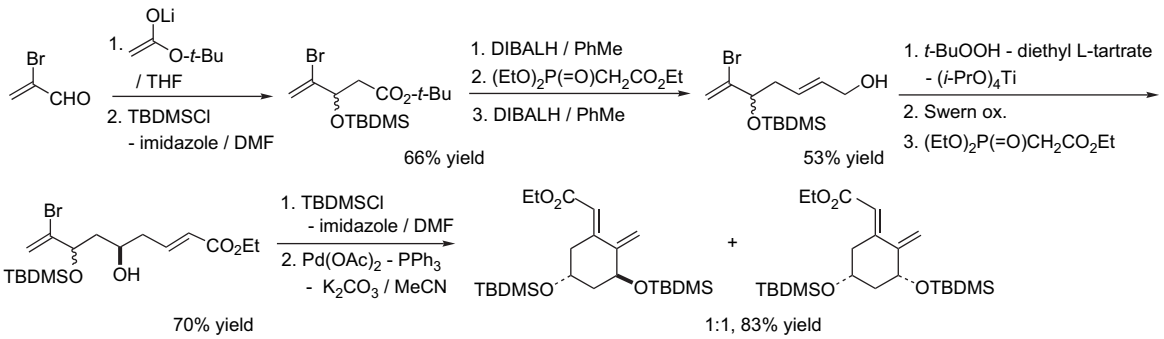
Trost proposed an original strategy to elaborate simultaneously the A-ring and the trienic system of 1α-hydroxyvitamin D_3, which consisted of performing a palladium-



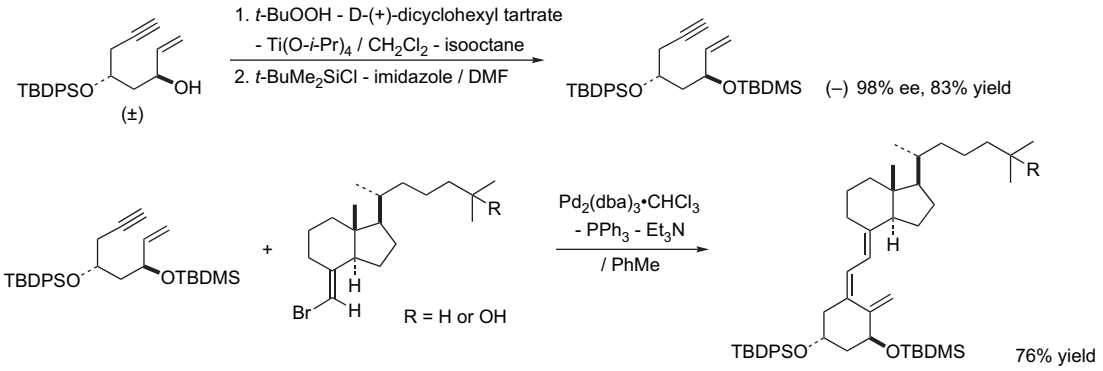
Scheme 156.



Scheme 157.



Scheme 158.

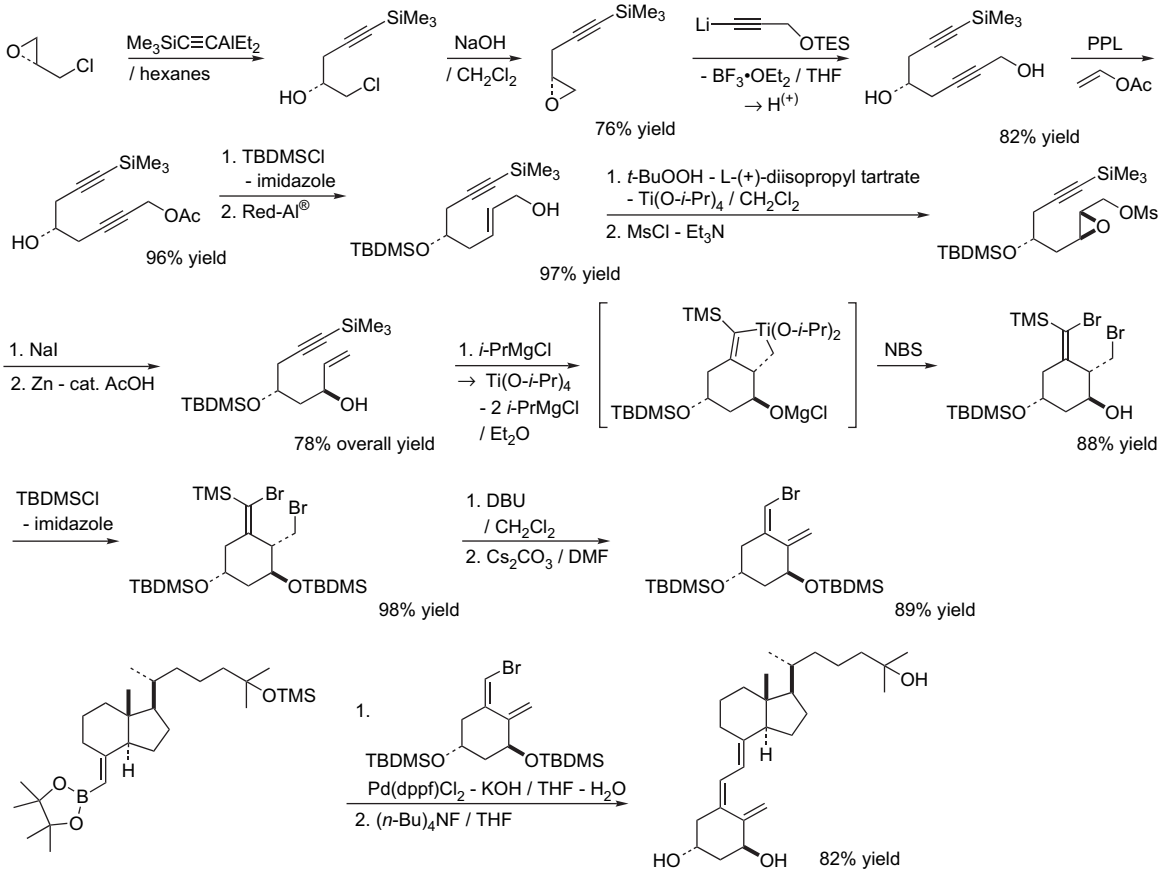


Scheme 159.

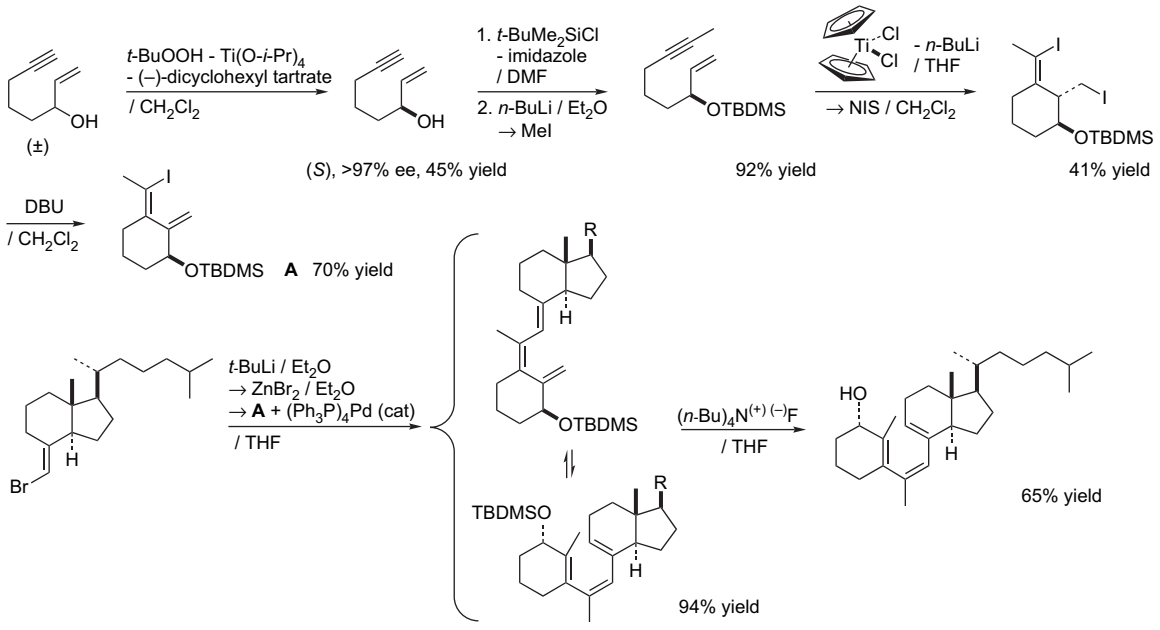
catalyzed alkylative tandem carbometalation–cyclization of a protected 1,7-enynediol[211] with the (*E*)-vinyl bromide derivative of Windaus–Grundmann ketone. The optically active starting acyclic enyne was obtained by Sharpless kinetic resolution of the racemic allylic alcohol, as presented in Scheme 159.[212]

Alternatively, 1α,25-dihydroxyvitamin D_3 could be synthesized by means of a Suzuki–Miyaura coupling between the corresponding bromodiene A-ring and alkenylboronate CD-ring fragments. Starting from the optically active epichlorhydrin, Sato prepared the A-ring precursor, in which the 1α-hydroxyl group was introduced by a Sharpless asymmetric epoxidation and the cyclic dienic system was constructed using a sequence of titanacyclization of the intermediate enyne and bromination followed by HBr elimination (Scheme 160).[213]

To obtain 6-methyl analogs of vitamin and previtamin D, Mouriño and co-workers based their approach on a zirconium-promoted cyclization–iodolysis of an acyclic 1,7-enyne as a key step. As mentioned previously, the linear precursor of the A-ring iododiene was subjected to Sharpless kinetic resolution, leading to the enantiomerically pure enynol. After HI elimination, a Negishi-type cross-coupling of the vinyl iodide with an alkenylzinc reagent bearing the CD-ring-side chain of vitamin D_3 provided the expected triene (Scheme 161).[214]



Scheme 160.



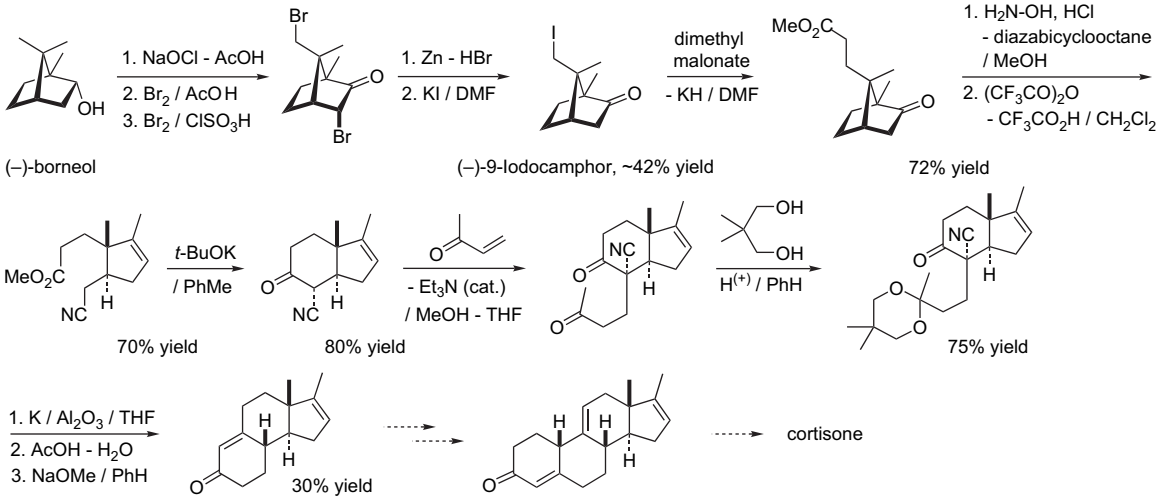
Scheme 161.

6. Use of molecules from the chiral pool

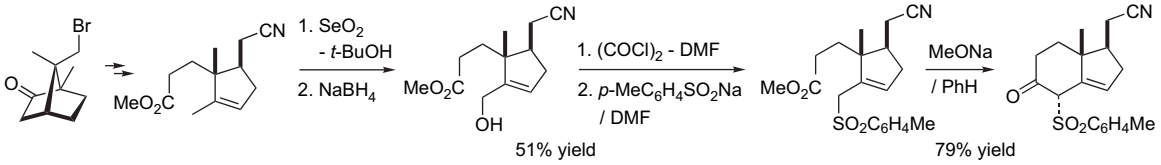
6.1. Use of camphor derivatives

Camphor is, undeniably, the cheapest compound of the chiral pool.[215] Somewhat surprisingly, there only two examples of steroid approaches involving camphor derivatives. In 1977, chiral intermediates for the enantioselective synthesis of steroids were elaborated by Stevens and co-workers starting from (−)-borneol as a source of (−)-camphor. The displacement of (−)-9-iodocamphor with an excess of the sodium salt of dimethyl malonate and its subsequent decarboxylation gave rise to the homologated keto ester. This latter compound underwent a sequence of reaction steps involving a Beckman fragmentation of the oxime ester to a cyano ester and a hybrid of the Zeigler and Dieckmann condensations. Treatment of the resulting *trans*-hydrindane with methyl vinyl ketone, removal of the cyano group, and then aldol condensation afforded the (+)-BCD tricycle as a potent precursor of cortisone (Scheme 162).[216a] Alternatively, the cyano ester derived from (+)-9-iodocamphor was regioselectively oxidized with selenium dioxide to afford the unstable aldehyde, which was readily reduced by sodium borohydride to an allylic alcohol and converted into the related sulfone. Treatment with sodium methoxide liberated the desired bicyclic hydrindanone (Scheme 163).[216b,c]

In a similar approach, Money and co-workers reported the enantioselective synthesis of estrone by ring cleavage of (+)-9,10-dibromocamphor. The resulting hydroxy acid was converted into the intermediate keto aldehyde, which underwent an intramolecular aldol condensation, generating the optically active *trans*-hydrindenone fragment. Regioselective conjugate addition of *m*-methoxybenzylmagnesium chloride to the vinylogous amide, stereoselective reduction of the cross-conjugated trienone with Li/NH_3 followed by

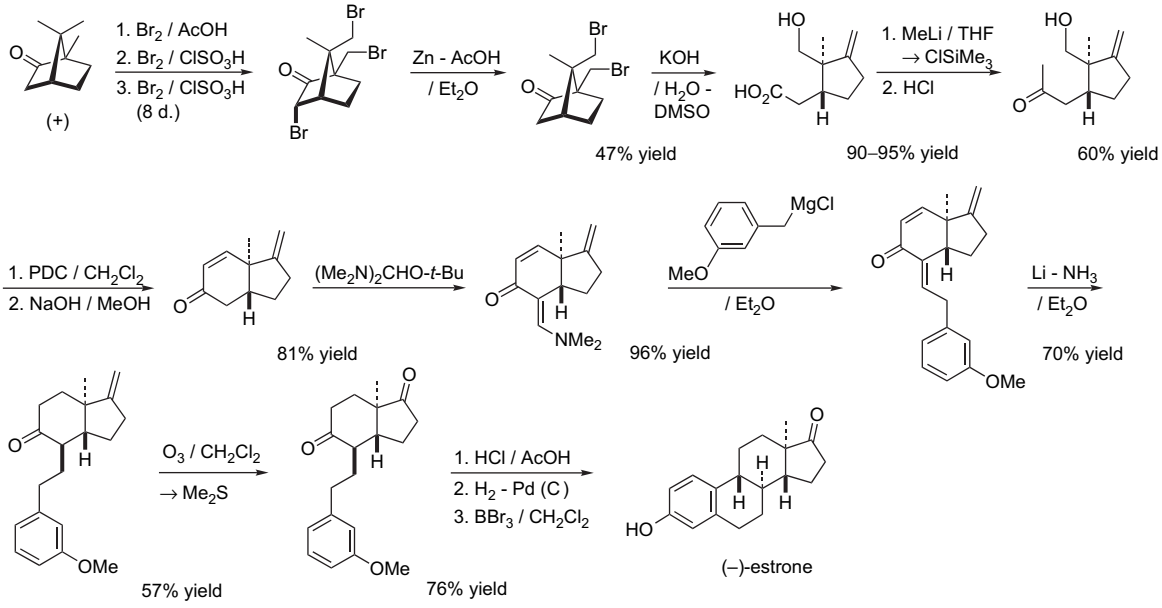


Scheme 162.

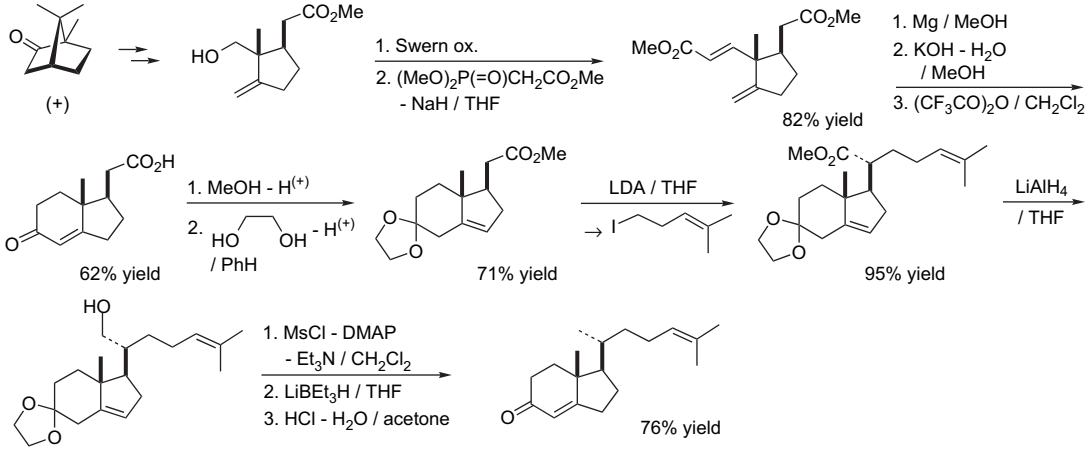


Scheme 163.

ozonolysis provided the known diketone. Subsequent acid-mediated cyclodehydration of the diketone, catalytic hydrogenation, and demethylation completed the approach to (−)-estrone (Scheme 164). Access to natural (+)-estrone would require the use of (−)-3-bromocamphor, which could be obtained by oxidizing (−)-borneol to (−)-camphor followed by bromination in acetic acid.[217] The introduction of a side chain unit present in a variety of steroids into the C(20) position was also considered by the authors. Starting from the previous D-ring synthon hydroxyl acid and, after a two-carbon homologation, cyclization of the corresponding diacid with trifluoroacetic anhydride followed by a methanolic work-up produced the hydrindenone ester, in which the chiral centers at C(13) and C(17) originated from (+)-9,10-dibromocamphor. Diastereoselective alkylation of the ketal ester enolate with 5-iodo-2-methylpent-1-ene on the less hindered face and reduction with $LiAlH_4$ provided the hydroxy ketal. Finally, further functional-group manipulations led to the hydrindenone bearing the steroidal side chain unit (Scheme 165).[218]



Scheme 164.



Scheme 165.

6.2. Use of carvone

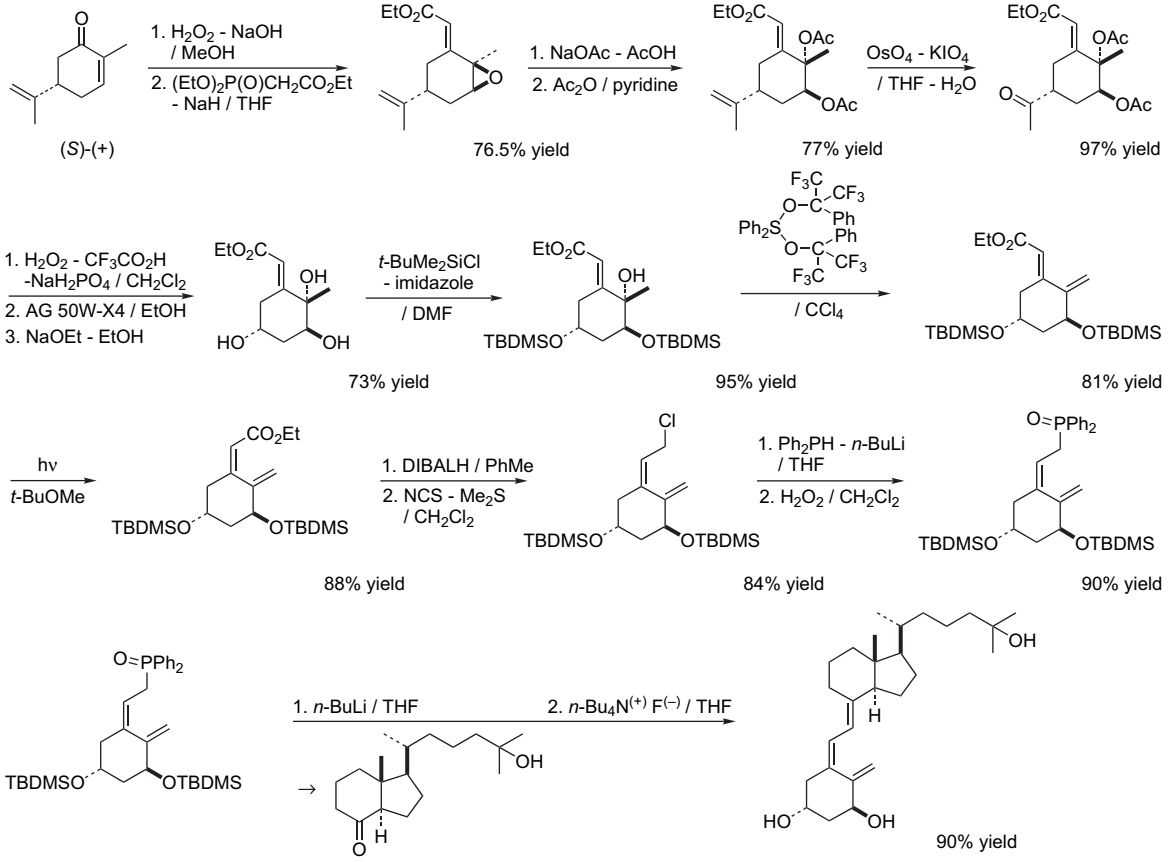
Carvone is currently the starting material of choice for the construction of the A-rings of the hormonally active 1α,25-dihydroxyvitamin D_3 and its analogs. The fact that both enantiomers are commercially available allowed the facile preparation of the natural A-ring and its optical image. In 1986, Baggiolini and co-workers from Hoffmann-La Roche were the first to achieve the chemical total synthesis of the optically active 1α,25-dihydroxycholecalciferol and 1α,25-dihydroxyergocalciferol involving the Lythgoe allylic phosphine oxide approach. An efficient 14-step procedure for the A-ring synthesis was proposed starting from (*S*)-(+)-carvone and with a 21% overall yield. The 1α-hydroxy function was readily introduced by stereospecific epoxide ring opening, while the other 3β resulted from an oxidative cleavage of the isopropenyl side chain and a subsequent Baeyer–Villiger rearrangement. One of the major difficulties has been the dehydration of the tertiary allylic alcohol to an *exo*-methylene group that could be carried out only with the Martin's sulfurane reagent. After photoisomerization, the dienoate ester was derivatized to the A-ring allylic phosphine oxide. The corresponding lithium carbanion was then added to the 25-hydroxylated Windaus–Grundmann ketone, which underwent a Wittig–Horner reaction and afforded 1α,25-dihydroxyvitamin D_3 (cf. Section 3.4.2.4) (Scheme 166).[219]

The 1α-fluoro analogs were also prepared by modifications of the preceding procedure, as depicted in Scheme 167. The key steps in the synthesis were the epimerization of the *trans*-acetoxy alcohol with (diethyl amido)sulfur trifluoride (DAST) to the cis-regioisomer and the stereospecific fluorination of the free alcohol with complete inversion of configuration.[220]

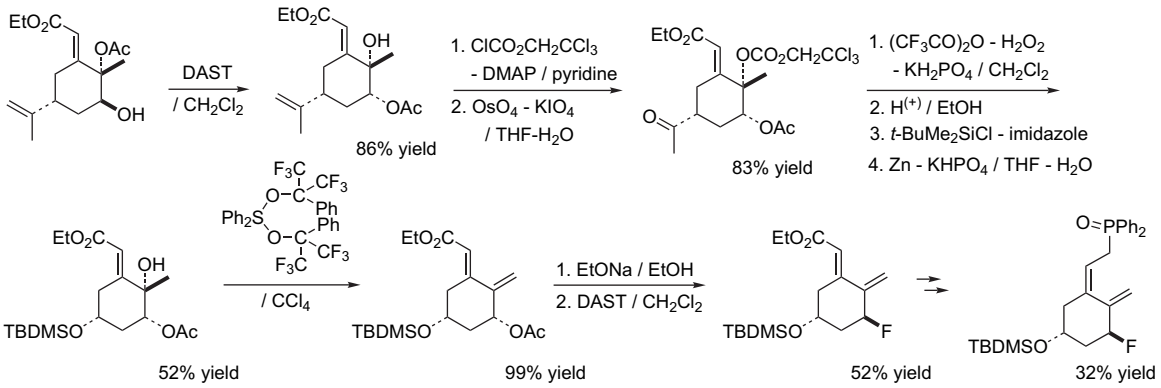
Radinov and co-workers improved considerably the seminal synthesis of the A-ring phosphine oxide by employing two novel efficient synthetic transformations. While oxidative degradation of the isoprenyl substituent was accomplished in three steps, the desired 3β-alcohol could be obtained by a one-pot procedure involving ozonolysis, Criegee rearrangement of the peroxyester intermediate,[221] and saponification of the acetate. An efficient chemo- and stereoselective palladium-catalyzed isomerization of the 1α-dienoxide (*E*)-ester led to the 1α-allylic alcohol with an exocyclic double bond.[222] Then, triphosgene chlorination and subsequent substitution with diphenylphosphine oxide[223] gave the A-ring phosphine oxide in only nine steps (Scheme 168).

The strong biological activity of 1α-fluoro-25-hydroxyvitamin D_3 stimulated Radinov's group to provide an efficient synthesis of the 1α-fluoro A-ring phosphine. Their approach centered on a stereoselective directed epoxidation of a tertiary allylic alcohol, a palladium-catalyzed isomerization of a diene oxide to a dienol followed by a fluorination with DAST (Scheme 169).[224]

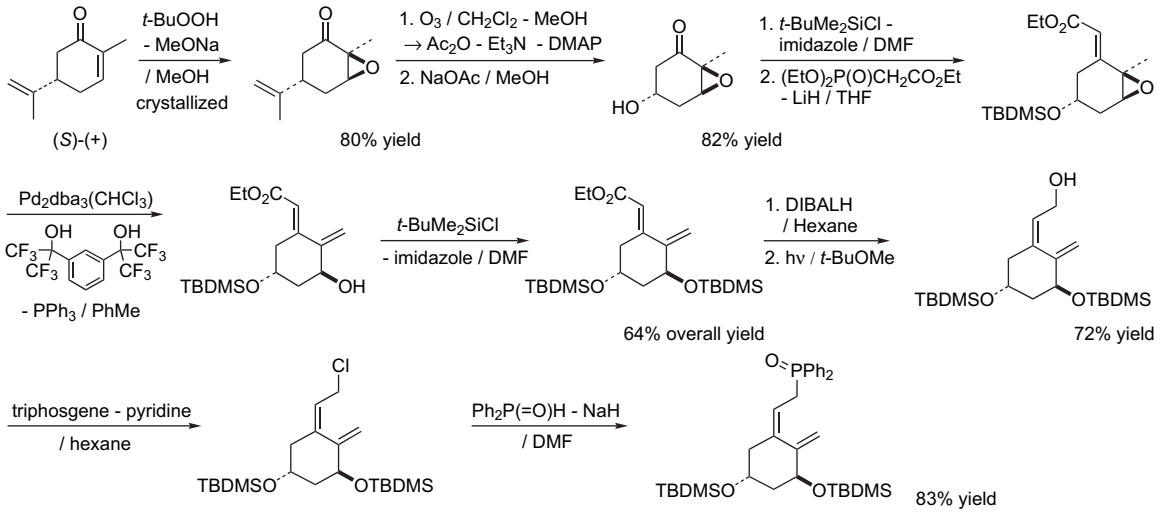
Masciadri and co-workers reported another route to the fluorinated A-ring precursor on a multigram scale that started by a regioselective *syn*-epoxidation of (+)-*cis*-carveol. Fluorine



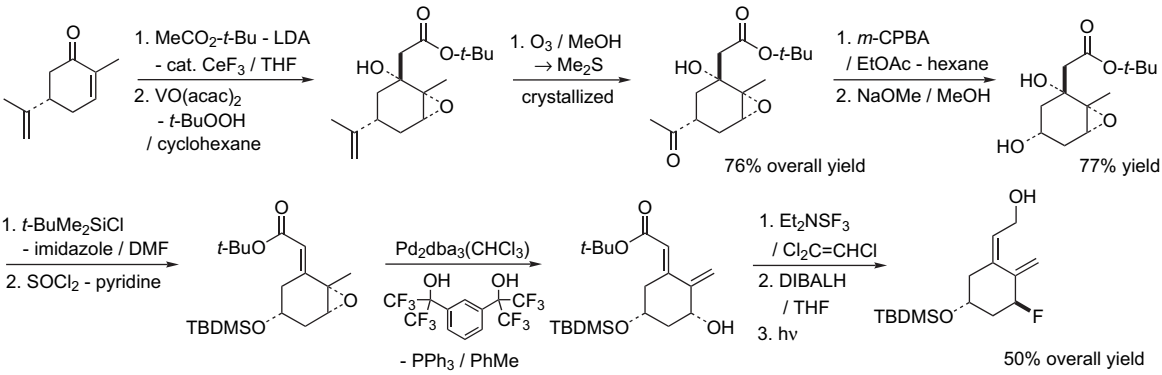
Scheme 166.



Scheme 167.



Scheme 168.

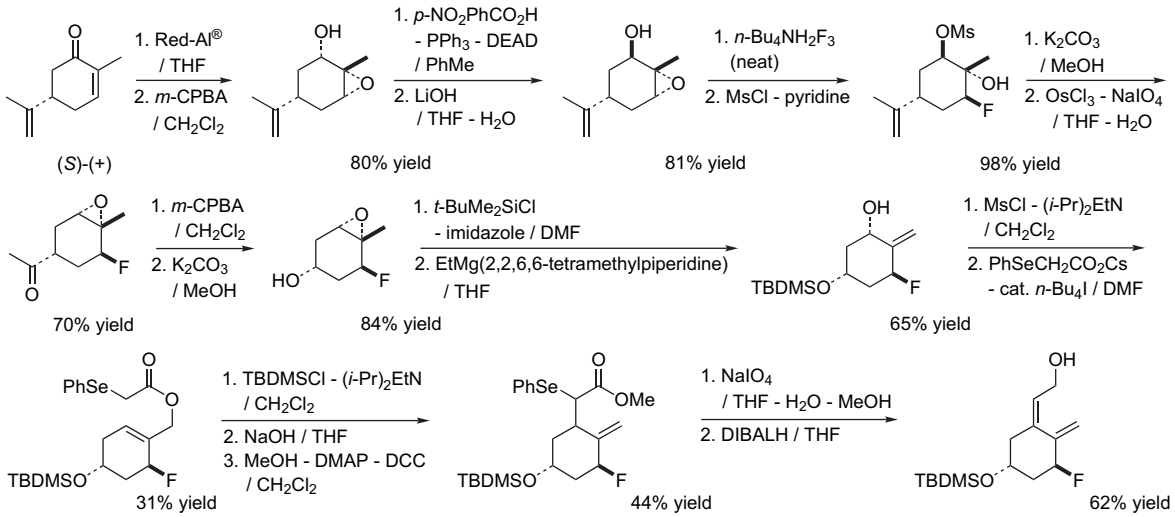


Scheme 169.

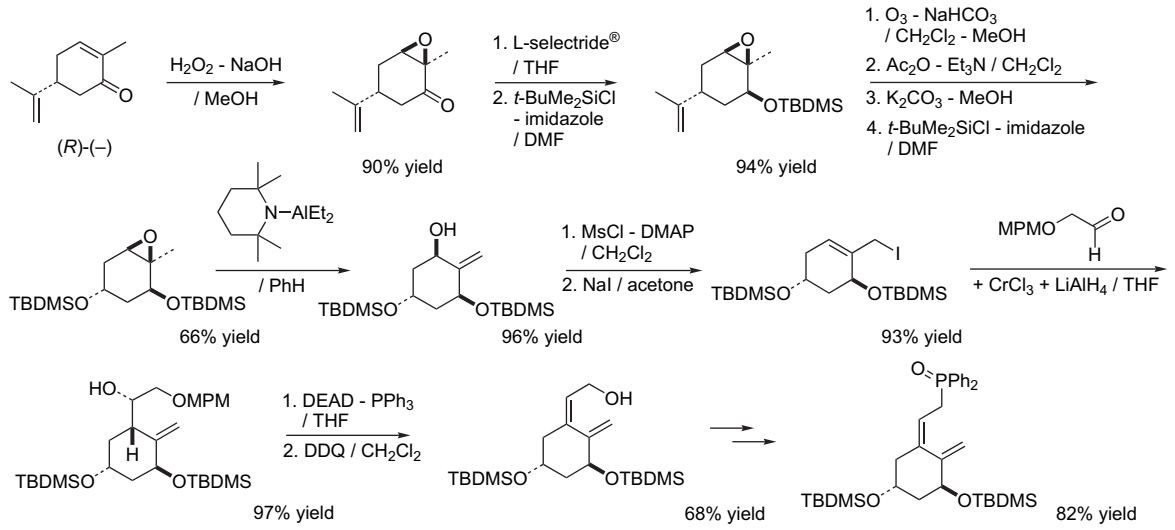
was introduced by *trans*-diaxial ring opening of the epoxide with $NBu_4NH_2F_3$ and the dienoate ester was elaborated from an advanced allylic alcohol intermediate via a sequential S_N' substitution with cesium phenylselanylacetate, Ireland–Claisen-type rearrangement of the resulting ester, and elimination of phenyl selenoxide (Scheme 170).[225]

For their part, Takano and co-workers showed that the key A-ring allylic phosphine oxide could be obtained by the use of a diastereoselective chromium(II)-mediated addition of an allylic iodide derived from (*R*)-(−)-carvone to aldehyde as a key step. The crucial construction of the conjugated diene A-ring part was then achieved by stereo- and regioselective dehydration of the resulting homoallylic alcohol through a trans elimination process (Scheme 171).[226]

Two years later, the same authors investigated a new convergent approach to the synthesis of (+)-1α,25-dihydroxyvitamin D_3 relying on a chromium(II)-mediated coupling of the preceding intermediate allyl iodide and the α,β-



Scheme 170.



Scheme 171.

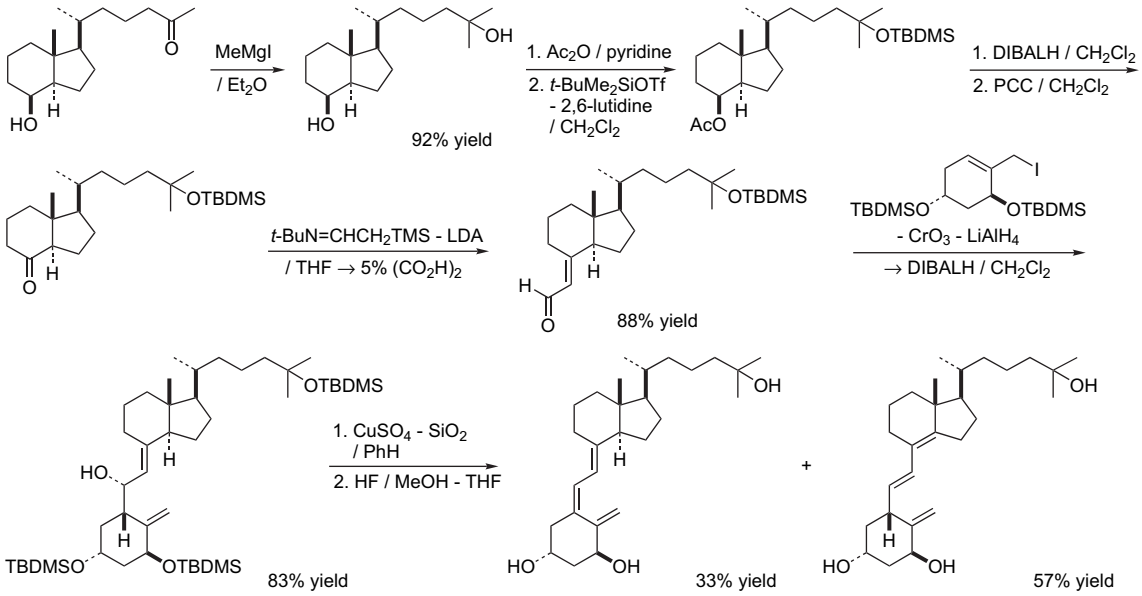
unsaturated aldehyde CD-ring fragment. The coupling reaction was highly diastereoselective, but the subsequent copper(II) sulfate-catalyzed dehydration converted the resulting alcohol into a mixture of vitamin D_3 metabolites with conjugated and unconjugated trienes (Scheme 172).[227]

Still from (*S*)-(+)-carvone, Baggiolini and co-workers developed a stereospecific synthesis of Lythgoe's A-ring dihydroxyaldehyde for the preparation of 1α-hydroxylated vitamin D_3 derivatives by using a Julia olefination procedure. The known carvone epoxide underwent a Darzens condensation followed by ozonolysis of the isopropenyl side chain and Criegee rearrangement of the intermediate peroxyester. Finally, a copper chromite-assisted decarboxylation and rearrangement of the epoxyglycidic acid generated both α,β-unsaturated aldehyde and 1α-hydroxy functions (Scheme 173).[228]

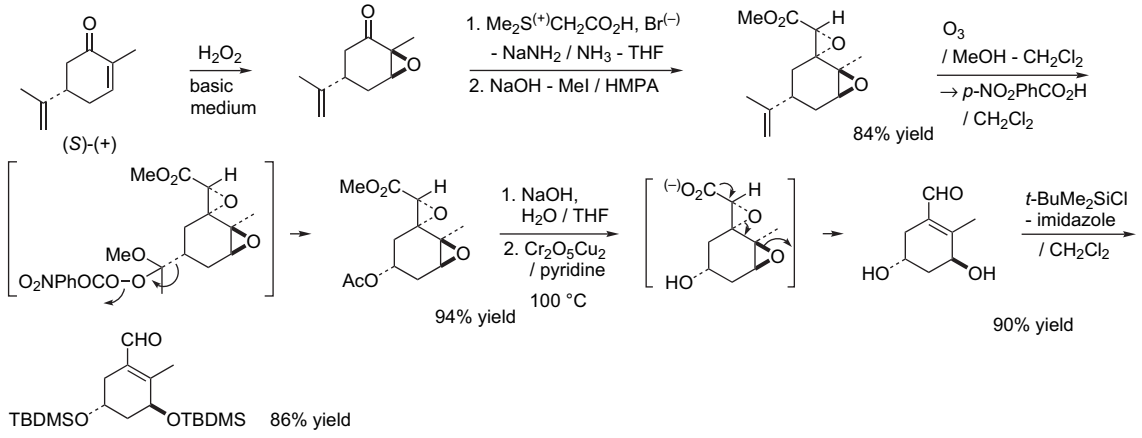
More recently, Mouriño and co-workers proposed an original strategy to access the A-ring synthon phosphine oxide, which involved an oxidative cleavage of a protected dihydroxy epoxide. The related acyclic dicarbonyl compound was further transformed into the familiar dienoate ester via a sequential Wittig reaction, vinyl triflate formation, and palladium-catalyzed cyclization–carbonylation (Scheme 174).[229]

Earlier, Castedo and co-workers were interested in the synthesis of a Lythgoe-type enyne diol, which could advantageously be coupled with a CD-bicyclic fragment such as the Windaus–Grundmann ketone. Starting from (*S*)-(+)-carvone, conversion of the derived ketone epoxide into homoallylic alcohol was accomplished using a combination of Wharton's reaction and [2,3]-sigmatropic rearrangement of a lithiated allylic stannyl ether. Hydroxyl-directed epoxidation of the transposed product restored the chirality at position C(1) and a chain extension to the enyne involved a Corey–Fuchs procedure (Scheme 175).[230]

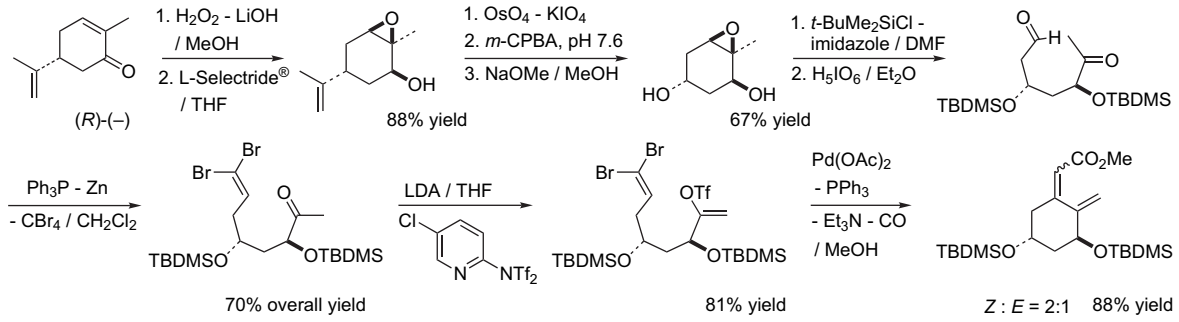
In their approach, Okamura and co-workers utilized as the key steps a stereoselective lithium acetylide addition to the carvone carbonyl group, a selective ozonolysis/Criegee



Scheme 172.

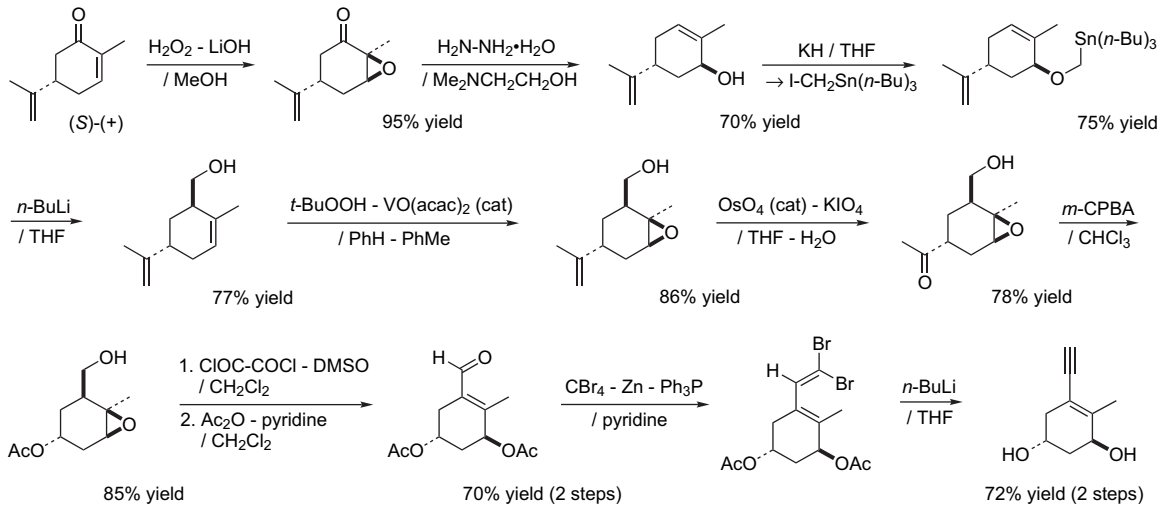


Scheme 173.

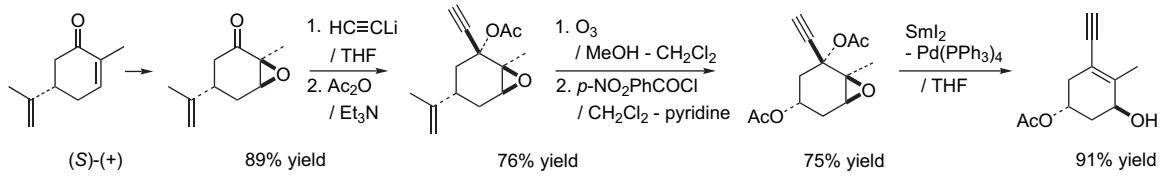


Scheme 174.

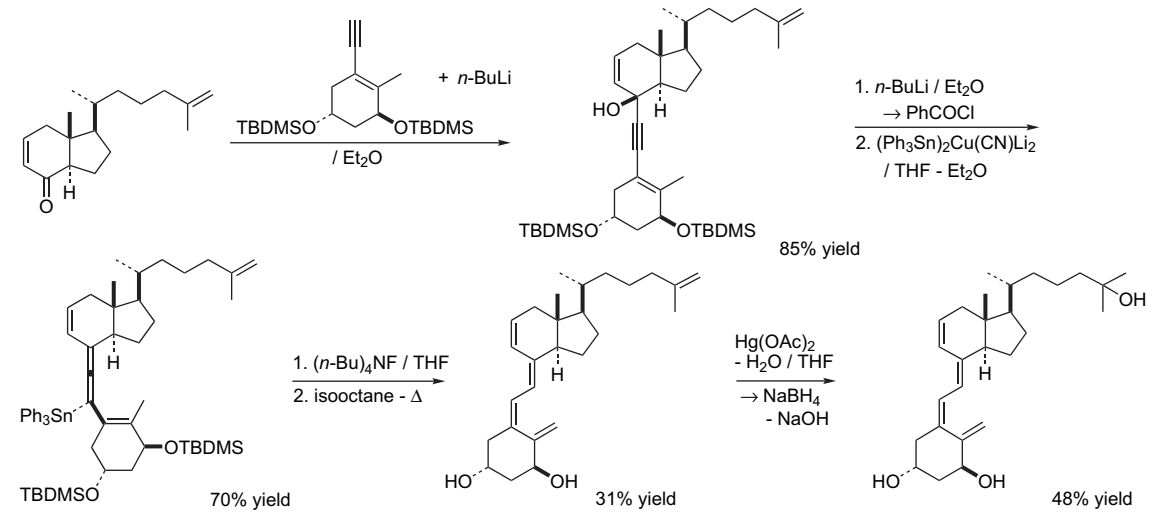
rearrangement, and an SmI_2/palladium-mediated reductive elimination of the epoxy propargyl acetate with concomitant epoxide ring opening to prepare the enyne diol (Scheme 176). From the latter diol, it was possible to synthesize 1α,25-dihydroxy-9,11-dehydrovitamin D_3 by coupling with the 9,11-dehydro bicyclic enone followed by stannylcuprate S_N2' displacement of the propargyl benzoate, selective fluorodestannylation of the vinylallene and a thermal [1,5]-sigmatropic hydrogen shift. The final oxymercuration–demercuration reaction then afforded the target molecule (Scheme 177).[231] Analogs of vitamin D_3 bearing an amino group at the C-1 or C-3 position have been prepared by Gotor, starting from the previous enyne acetate A-ring fragment.[232]



Scheme 175.



Scheme 176.

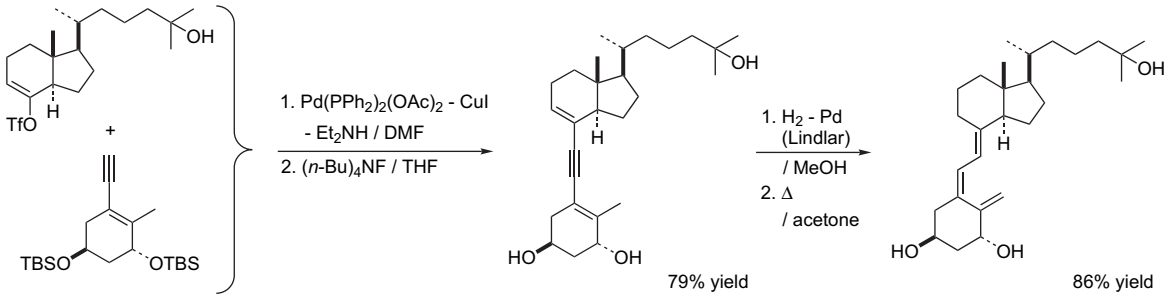


Scheme 177.

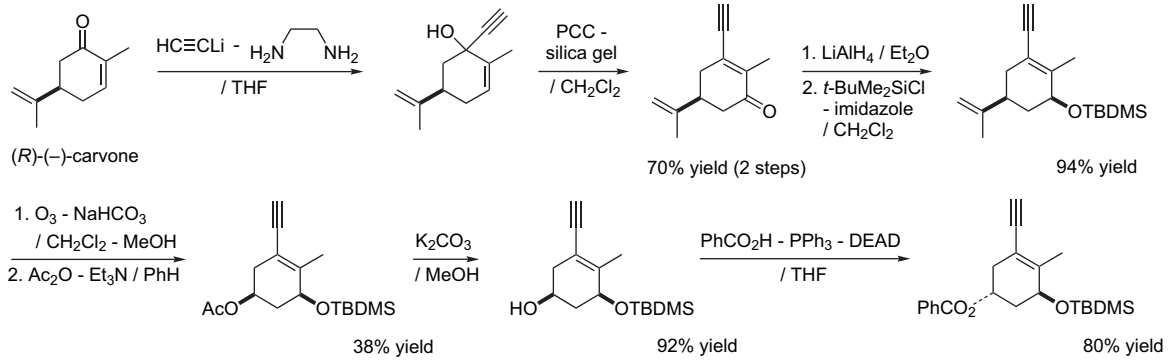
An alternative method for coupling the A- and CD-ring fragments, developed by Mouriño[233] and applied by Okamura,[234] comprised a palladium-catalyzed cross-coupling reaction of the enynol with the CD-ring triflate. The corresponding trihydroxydienyne could undergo catalytic hydrogenation and thermal [1,7]-sigmatropic hydrogen shift/isomerization (Scheme 178).

In 2000, Srikrishna and co-workers suggested a direct approach to the opposite enantiomer of the enynol A-ring precursor starting from (*R*)-(−)-carvone. The acetylenic side chain was conveniently introduced by employing a 1,3-enone transposition methodology and the controlled ozonolysis/Criegee rearrangement sequence led to the corresponding 1α,3α-A-ring. The Mitsunobu inversion of the 3α- into 3β-alcohol should allow the formation of the *ent*-calcitriol (Scheme 179).[235]

Finally, a short synthesis of an enantiomerically pure tetracyclic CD *cis* coupled D-homo steroid skeleton was developed by de Groot and co-workers. Their strategy relied on a $TrSbCl_6$-mediated Mukaiyama–Michael reaction of the silyl enol ether of methoxytetralone with (*R*)-(−)-carvone, in which the silyl group was transferred to the accepting enone.



Scheme 178.



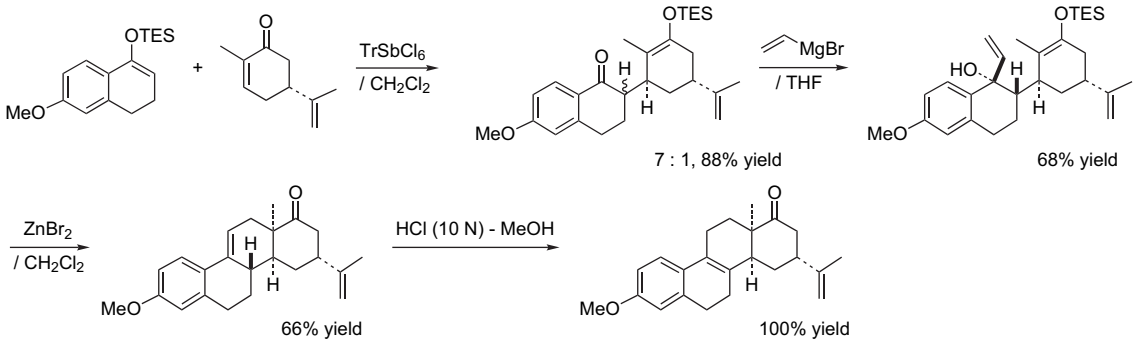
Scheme 179.

Addition of vinylmagnesium bromide gave the Torgov-type intermediate, the carbocation of which, generated in the presence of $ZnBr_2$, could react with the new silyl enol ether with the natural steroid configuration at C(14). Closure of the C-ring then led to a cis-fused CD-ring system with the natural steroid configuration at C(14) (Scheme 180).[236]

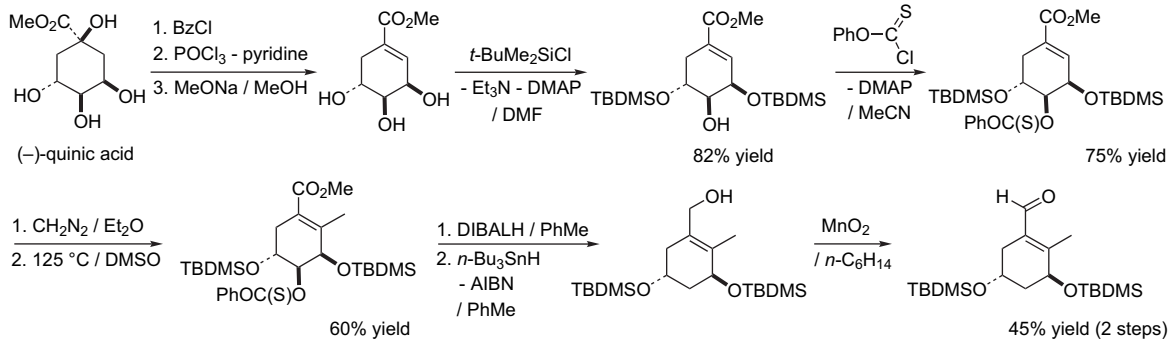
6.3. Use of quinic acid

D-(−)-Quinic acid, a commercially available cheap starting material, possesses interesting (3*R*,5*R*)-1,3-dihydroxy and α-hydroxy acid functions essential in the preparation of A-ring precursors of 1α,25-dihydroxyvitamin D. In 1985, Desmaele and Tanier were the first to achieve the synthesis of the A-ring synthon conjugated aldehyde, already described by Lythgoe, starting from this natural building block. This involved a radical Barton–McCombie deoxygenation of the C-2 hydroxyl group followed by introduction of the 19-methyl substituent with diazomethane as the key steps. (−)-Methyl shikimate obtained from D-(−)-quinic acid according to Gaudemer's methodology[237] was selectively protected with *tert*-butyldimethylsilyl chloride at C(3) and C(5). The remaining free hydroxyl was converted into thionocarbonate and the alkene moiety was submitted to a [2,3]-dipole cycloaddition of diazomethane. Then, pyrolysis of the resulting pyrazoline, a tandem DIBALH/radical reduction, and subsequent allylic oxidation led to the desired A-ring α,β-unsaturated aldehyde (Scheme 181).[238]

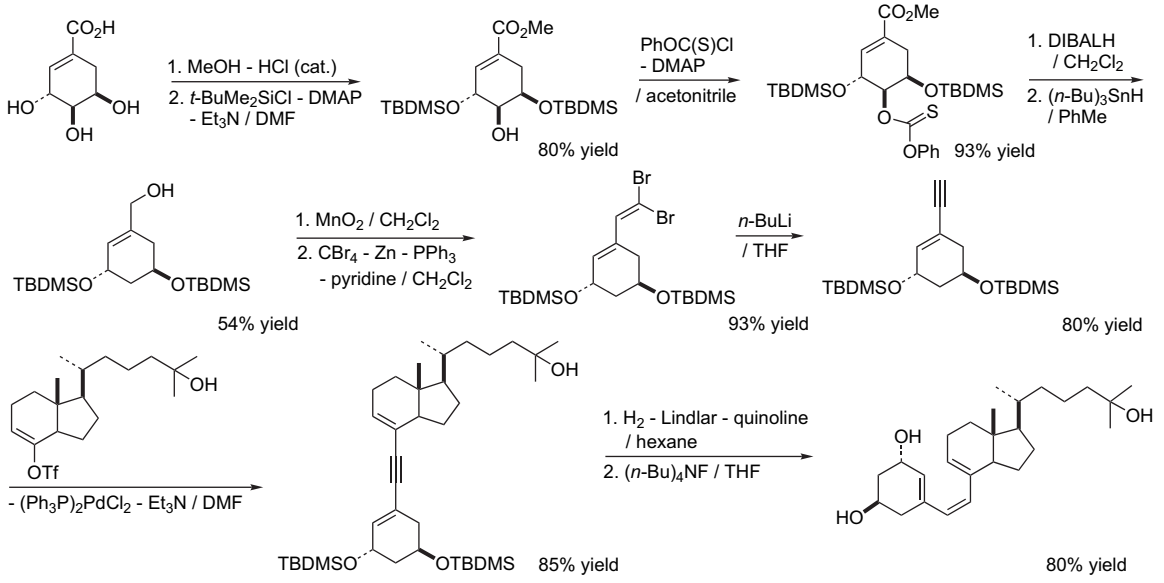
Following a similar strategy, Mouriño and co-workers have prepared an A-ring enyne synthon for the synthesis of 1α,25-dihydroxy-19-nor-previtamin D_3. The 19-nor analog of the previous α,β-unsaturated aldehyde intermediate was subjected to a Corey–Fuchs reaction in order to generate the desired enyne diol (Scheme 182), while Gotor's group preferred to synthesize it by the action of the lithiated trimethylsilyldiazomethane (Scheme 183). A selective desilylation of the α,β-unsaturated ester intermediate at C(1) and its



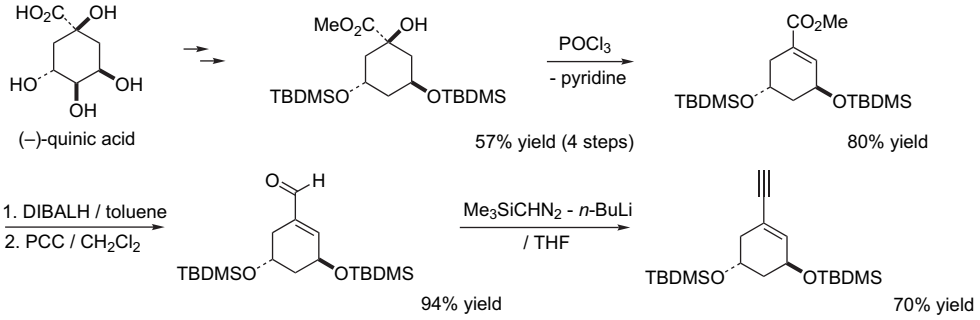
Scheme 180.



Scheme 181.



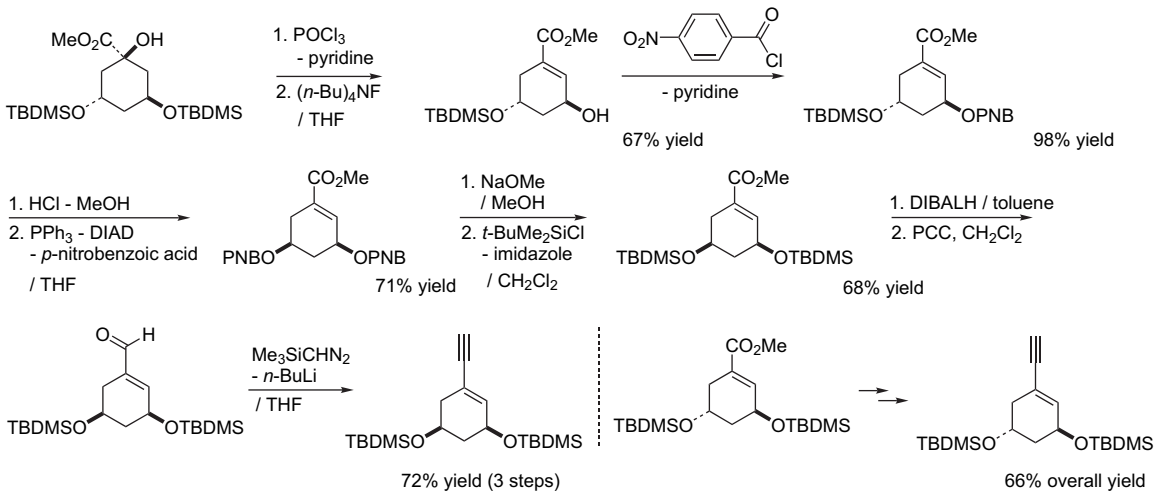
Scheme 182.



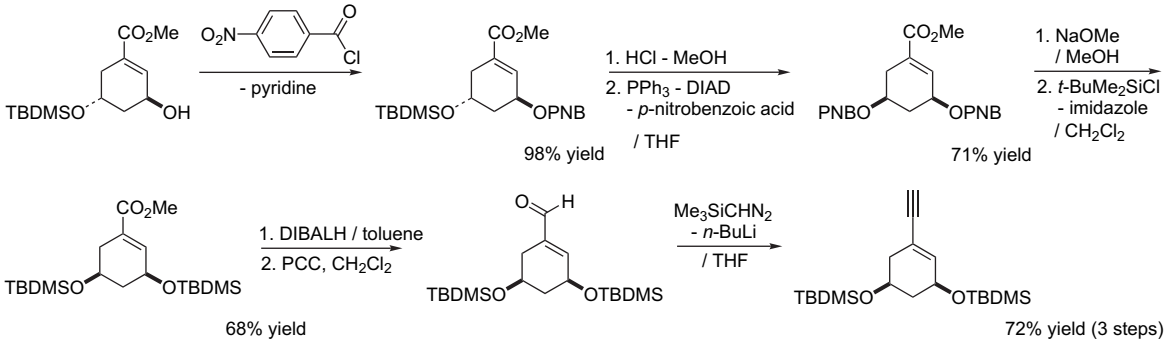
Scheme 183.

subsequent Mitsunobu inversion enabled access to the 1-*epi* adduct (Scheme 184). When the monoprotected compound was converted into the corresponding *p*-nitrobenzoate ester, the configuration of the alcohol at C(3) could be inverted under Mitsunobu conditions, giving, this time, the 3-*epi* derivative (Scheme 185). Thus, palladium coupling of each enyne with the known CD-ring/side chain vinyl triflate afforded novel 6-*s*-*cis* pre-D locked analogs of the steroid hormone, calcitriol.[239,240]

A slightly different procedure, reported by DeLuca, offered another route to build 19-nor-vitamin D compounds from a novel C_2-symmetric A-ring unit accessible by using D-(−)-quinic acid as a starting material. The main transformation concerned the degradation of the α-hydroxy acid function into a ketone through a sequential reduction of the ester group to allylic alcohol and oxidative cleavage with $NaIO_4$. As usual, removal of the 2-hydroxyl group proceeded by selective protection of the 1,3-diol followed by

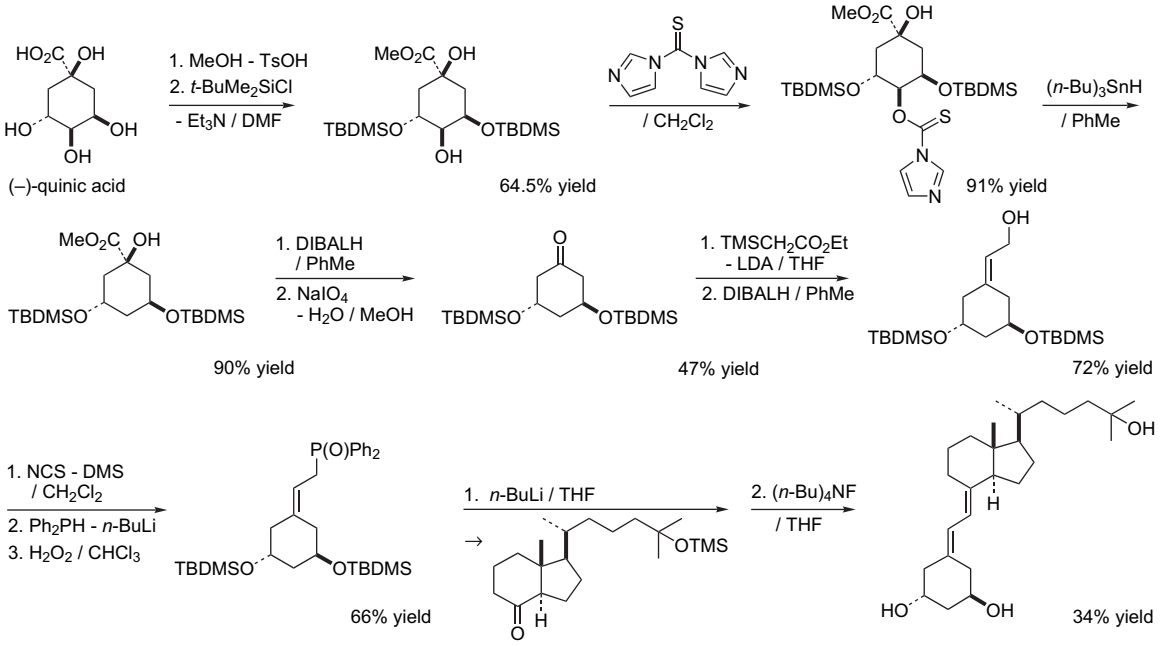


Scheme 184.

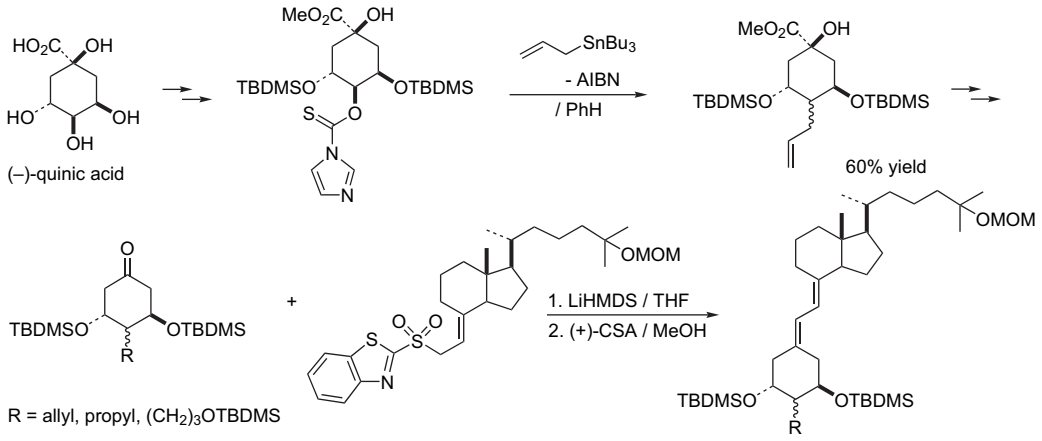


Scheme 185.

radical deoxygenation at C(4). Then, the allylic phosphine oxide system was installed on the resulting C_2-symmetric ketone and the lithio anion engaged in a Horner–Witttig reaction with the CD-ring Windaus–Grudmann ketone. The 1α,25-dihydroxy-19-nor-vitamin D_3 was isolated in 34% yield (Scheme 186).[241]



Scheme 186.

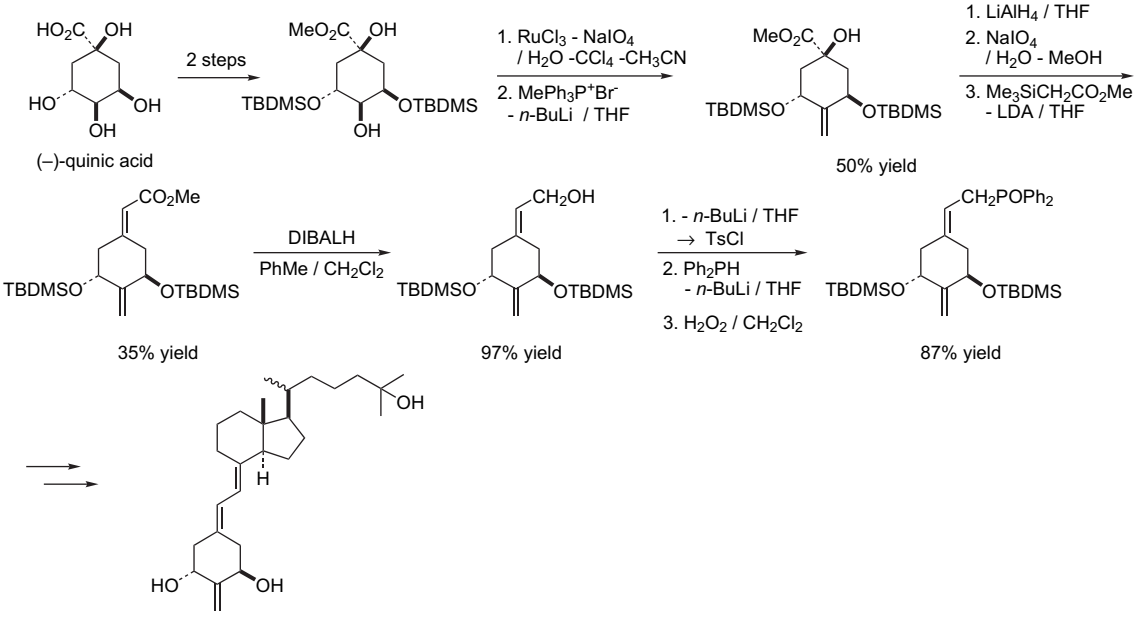


Scheme 187.

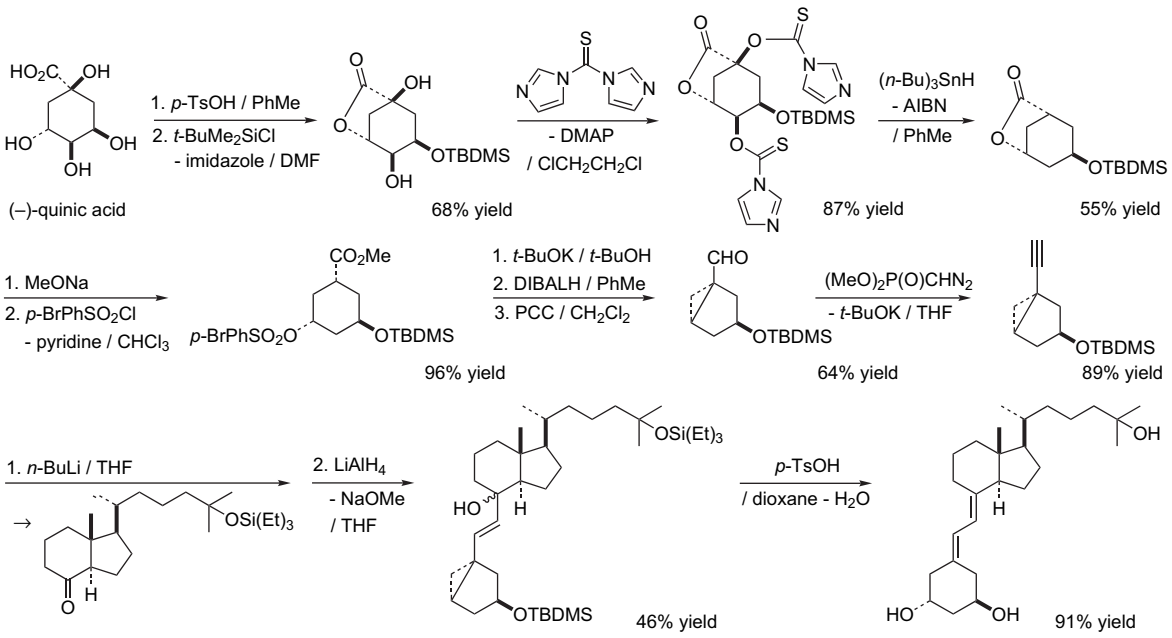
Radical Keck allylation instead of reduction of the previous thioimidazolide allowed the functionalization of the A-ring precursor at the C(2)-position. Further transformations of the resulting methyl allylquinicate led to 2-alkylated (3*R*,5*R*)-3,5-dihydroxy-cyclohexanones, which could undergo a Julia–Kocienski olefination with a CD-ring allyl sulfone in order to construct the diene unit of a series of 2-modified 19-nor-1α,25-dihydroxyvitamin D_3. The 2α-(3-hydroxypropyl) group contributed to a marked increase in both the VDR (vitamin D receptor) binding affinity and potency in the induction of HL-60 cell differentiation (Scheme 187).[242]

New 19-nor analogs of the natural hormone possessing an exomethylene group at the 2-position were prepared via a Lythgoe-type Wittig–Horner coupling approach. DeLuca and co-workers first described a synthetic route to the phosphine oxide A-ring synthon from (−)-quinic acid, which involved a selective oxidation/olefination of the secondary alcohol at C(2) and oxidative cleavage of a transient vicinal diol at C(5) to cyclohexanone followed by its Peterson olefination. After coupling with (20*R*)- and (20*S*)-25-hydroxy Grundmann ketones, these 2-methylene-19-norvitamins were converted into the 2-methyl and 2-hydromethyl derivatives.[243] Additionally, 2-ethyl and 2-ethylidene analogs were also synthesized four years later (Scheme 188).[244]

Vandewalle and co-workers exploited the potential of the Wilson strategy, based on acid-catalyzed sigmatropic rearrangement of cyclopropylic alcohol into homoallylic alcohol, to prepare 19-nor-1α-25-dihydroxyvitamin D_3 and related analogs. The requisite enantiomerically pure A-ring cyclopropyl acetylene was obtained from D-(−)-quinic acid by first selective protection of the hydroxyl groups at C(1) and C(3) as silylated ether and lactone derivatives, respectively, and removal of the remaining secondary and tertiary alcohol at C(2) and C(6) through a Barton–McCombie deoxygenation involving reduction of bis-thiocarbonyl imidazolides. Subsequent to brosylate formation, intramolecular alkylation of the ester enolate gave the bicyclic ester,



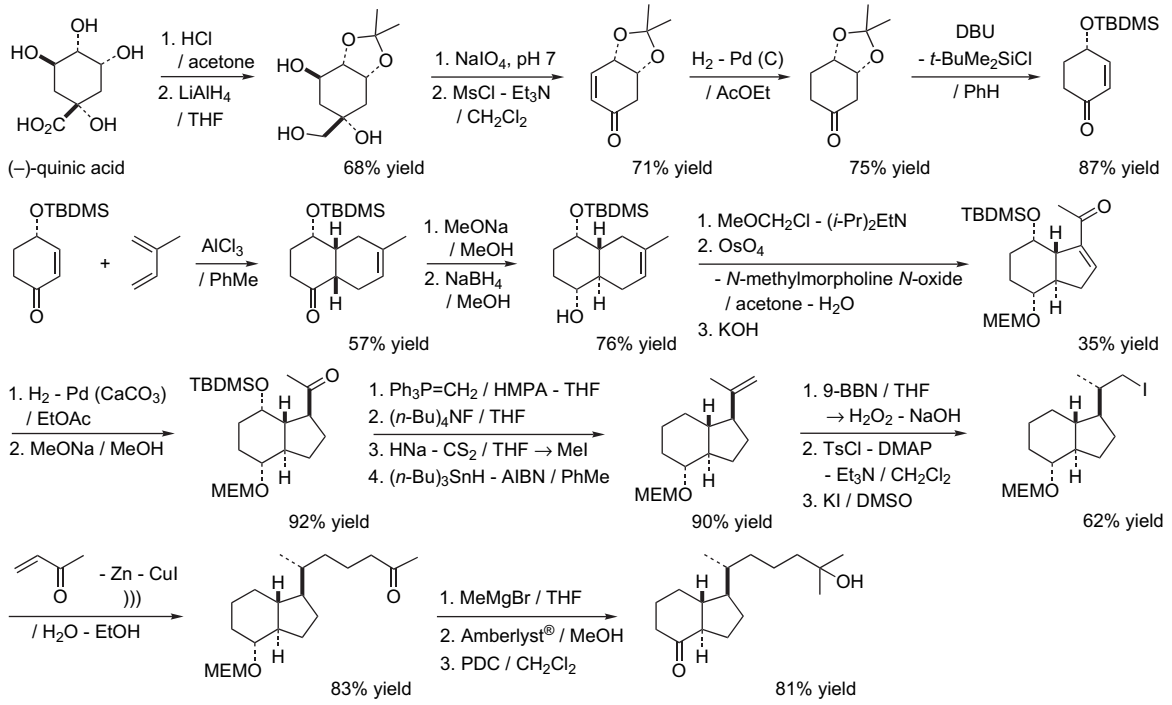
Scheme 188.



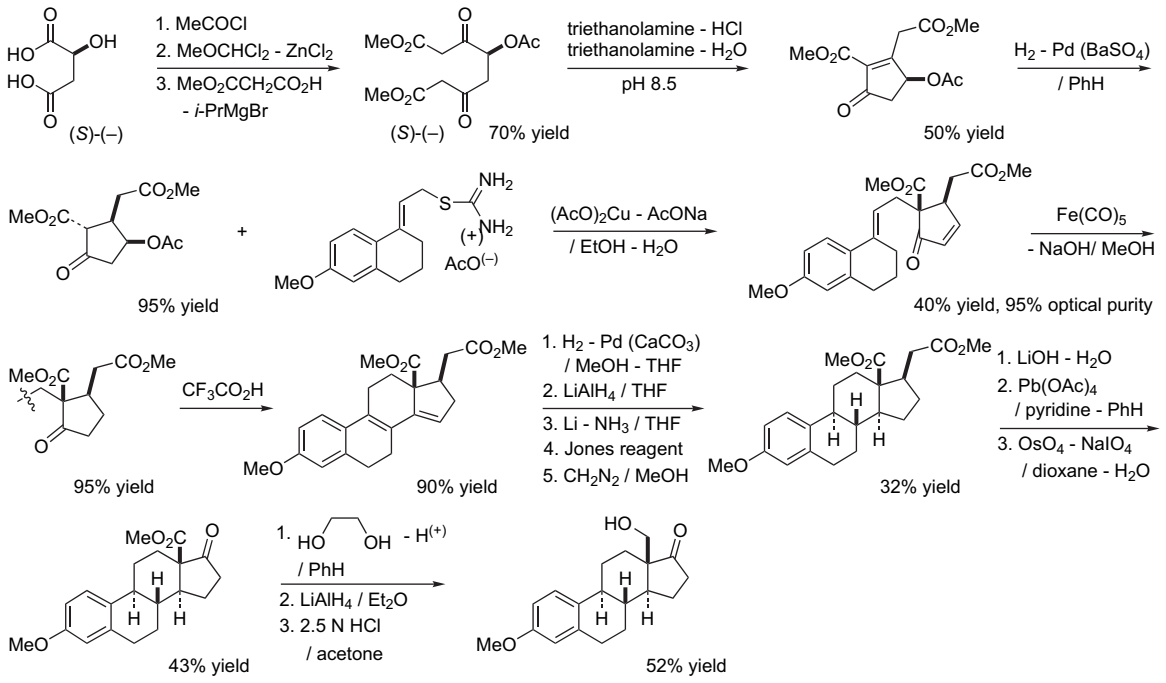
Scheme 189.

which was successively converted into aldehyde and alkyne via Seyferth's method to furnish the 19-nor A-ring precursor. Addition of the corresponding lithium acetylide to the 25-hydroxy Windaus–Grudmann ketone liberated the intermediate propargylic alcohol, which was reduced to the (*E*)-allylic alcohol. Acid-catalyzed solvolysis of this latter alcohol furnished 19-nor-1α-25-dihydroxyvitamin D_3 in moderate yield (Scheme 189).[245]

In connection with his researches on vitamin D analog synthesis, Vandewalle took advantage of the (*S*)-4-hydroxy-2-cyclohexenone, easily available from D-(−)-quinic acid,[246] to elaborate the 25-hydroxy-19-nor Windaus–Grudmann ketone. His strategy involved a Lewis acid-catalyzed intermolecular Diels–Alder reaction of the enone with isoprene followed by an interesting *cis*-decalin to *trans*-hydrindane transformation. The cycloaddition step led regioselectively to a 3:1 mixture in favor of the *syn*-adduct. Epimerization to *trans*-fused decalone and ring contraction provided the *trans*-hydrindane intermediate. After further transformations, the 18-nor CD-ring ketone could be coupled with an A-ring synthon phosphine oxide precursor (Scheme 190).[247]



Scheme 190.



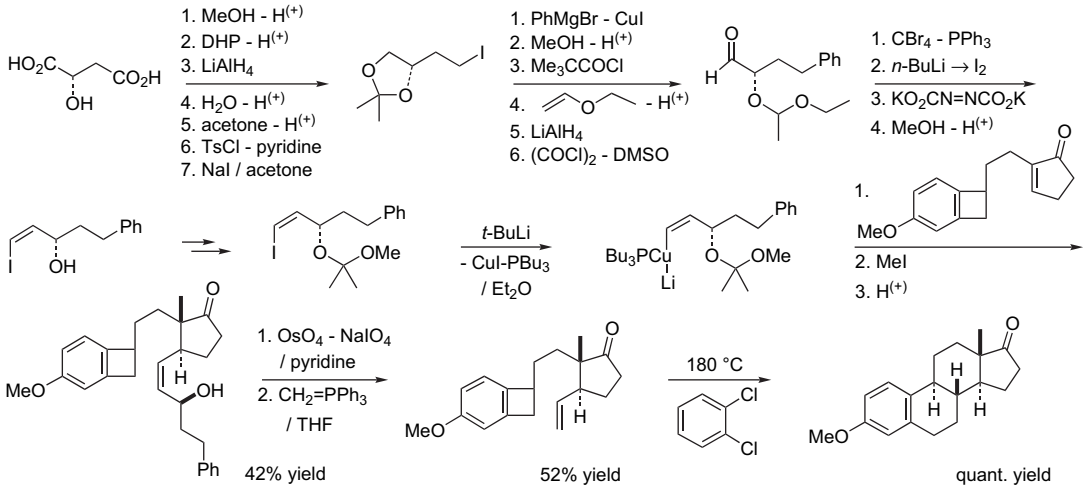
Scheme 191.

6.4. Use of malic acid

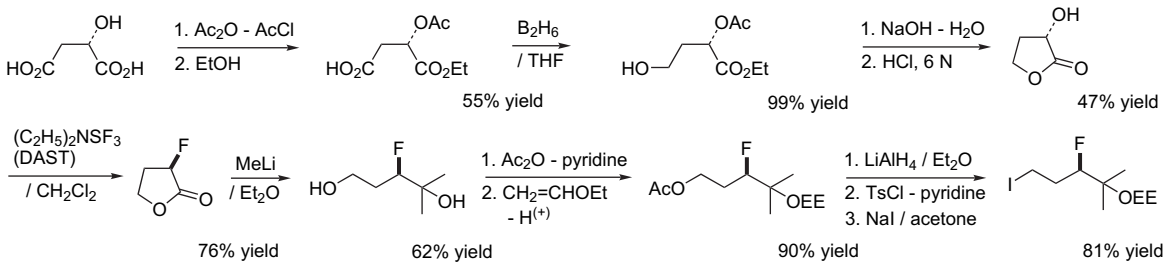
In 1976, Jonhson and co-workers reported the synthesis of an optically active β-keto ester derived from L-(+)-malic acid and used in the elaboration of natural prostaglandins such as (+)-$PGF_{2\alpha}$.[248] Later, this compound was also demonstrated to be a valuable synthetic intermediate in the construction of (+)-18-hydroxyestrone. Indeed, alkylation of its Cu(II) chelate by the modified Torgov steroid precursor isothiouronium acetate in aqueous ethanol gave the 8,14-secosteroid in which the acetoxy group has been eliminated. Reduction of the enone by the Noyori procedure and its subsequent cyclocondensation under acidic conditions furnished the tetracyclic steroid skeleton depicted in Scheme 191 as a key intermediate for the synthesis of C-18 functionalized steroids, e.g., (+)-18-hydroxyestrone.[249]

A highly enantioselective conjugate addition of an alkenylcopper/phosphine complex to a (±)-2-substituted cyclopentenone, a methylation of the transient enolate followed by an intramolecular Diels–Alder reaction with the *o*-quinodimethane were the pivotal steps in the synthesis of estrone methyl ether and its 7-alkylated derivative proposed by Takahashi and co-workers. The phosphine-stabilized organocopper reagent, prepared from an L-(+)-malic acid-derived vinyl iodide, added to the enone with a high level of enantioselectivity and provided exclusively the natural *trans-anti-trans* steroid adduct by the cycloaddition (Scheme 192).[250]

Hoffmann-La Roche investigations by Shiuey and co-workers have enabled the elaboration of a triply convergent approach to the stereoselective synthesis of 1α,25-dihydroxy-24(*R*)-fluorocholecalciferol. The interesting features of this strategy were the use of L-(+)-malic acid to introduce



Scheme 192.



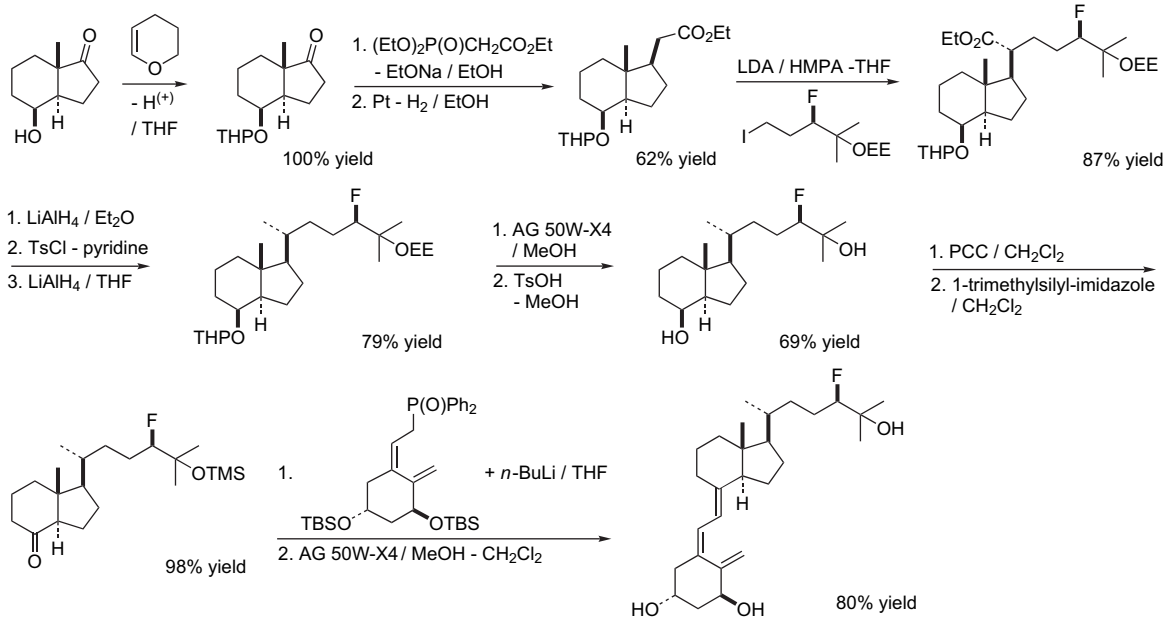
Scheme 193.

the chirality at C(24) of the side chain (Scheme 193), the Wicha alkylation[132] of the ester CD-ring synthon with the side chain in position 20 giving predominantly the natural configuration at C(20), and the Lythgoe coupling with the A-ring phosphine oxide described in Section 3.4.2.4. Utilizing the DAST reagent, the C-24 hydroxyl group borne by the side chain was cleanly substituted by a fluorine atom with a total inversion of configuration (Scheme 194).[251]

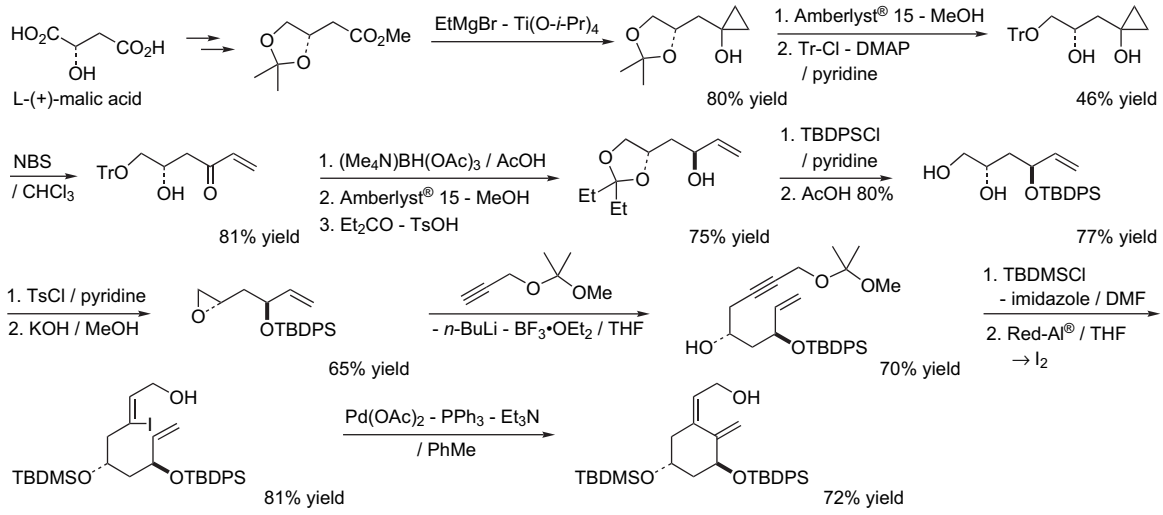
Wicha and co-workers proposed another synthetic route for the optically active A-ring allylic alcohol required in the 1α,25-dihydroxyvitamin D synthesis starting from L-(+)-malic acid. As an alternative to their previous approach based on a Sharpless epoxidation of 3-triphenylsilylglycidol and reported in Section 5, the authors elaborated a similar substituted epoxide by transforming the ester derived from L-(+)-malic acid into a cyclopropanol derivative with the use of the Kulinkovich cyclopropanation method.[252] The cyclopropanol moiety underwent a bromonium ion-induced rearrangement, and the resulting hydroxyketone was reduced to the *anti* diol and converted into the epoxide. Its nucleophilic ring opening with lithium acetylide gave the enyne diol, the corresponding vinyl iodide of which cyclized under Heck reaction conditions (Scheme 195).[253]

6.5. Use of diethyl tartrate

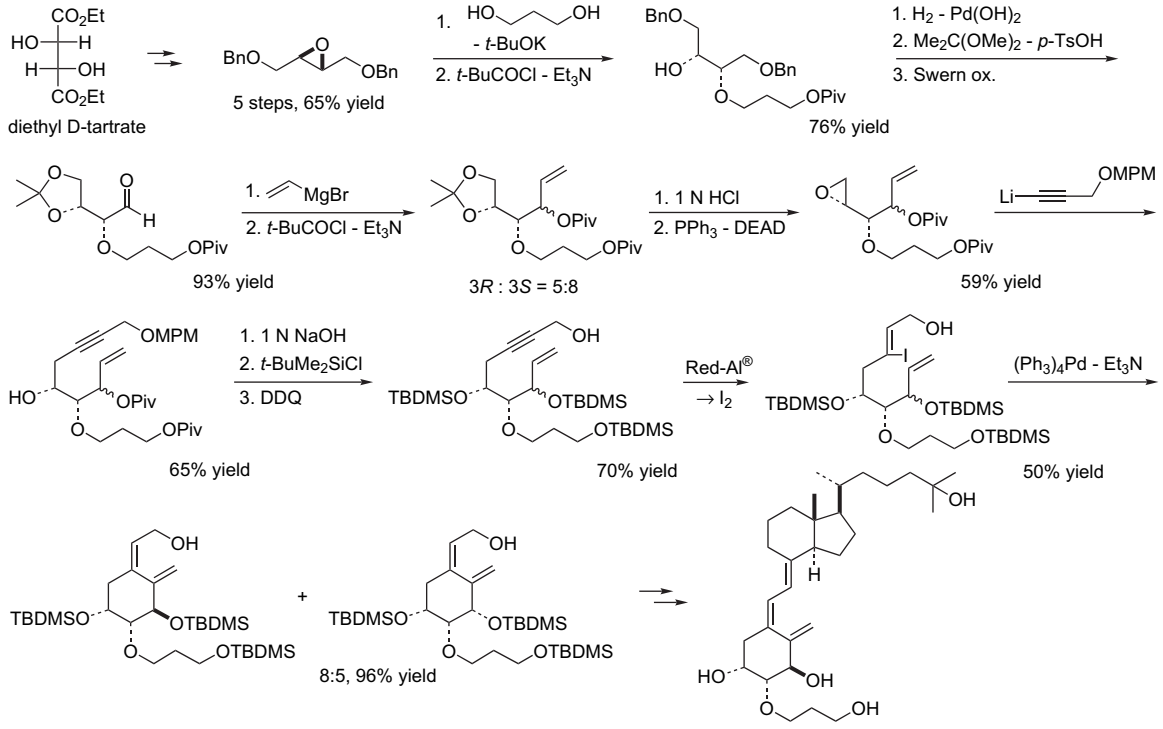
In 1997, Hatakeyama and co-workers reported the synthesis of 1α,24,25-trihydroxy-2β-(3-hydroxypropoxy)vitamin D_3 (ED-71), a potent analog of the active 1α,25-dihydroxyvitamin D_3 bearing a hydroxypropoxy group in position 2β and characterized by a highly calcemic activity and a long half-life in plasma. For the construction of the 2-modified A-ring precursor, they adopted the preceding enyne formation approach using a new dihydroxylated terminal epoxide intermediate and a similar Heck coupling reaction of a transient iodo derivative. Hence, elaboration of the acyclic enyne triol was realized through basic functional-group manipulations of the well-known C_2 symmetric epoxide, already prepared from (−)-diethyl D-tartrate by Nicolaou.[254] The Wittig–Horner reaction between the phosphine oxide and the CD-ring synthon, obtained from the Inhoffen–Lythgoe diol, furnished ED-71 (Scheme 196).[255] Alternatively, the transient terminal epoxide underwent a regioselective ring opening with lithium trimethylsilylacetylide (Scheme 197). The formed 1,7-enyne was involved in a palladium-catalyzed alkylative cyclization reaction with the CD-ring fragments and applied for the synthesis of ED-71 and 24-hydroxylated ED-71.[256]



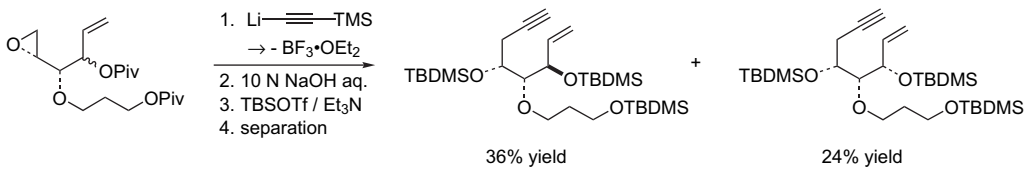
Scheme 194.



Scheme 195.



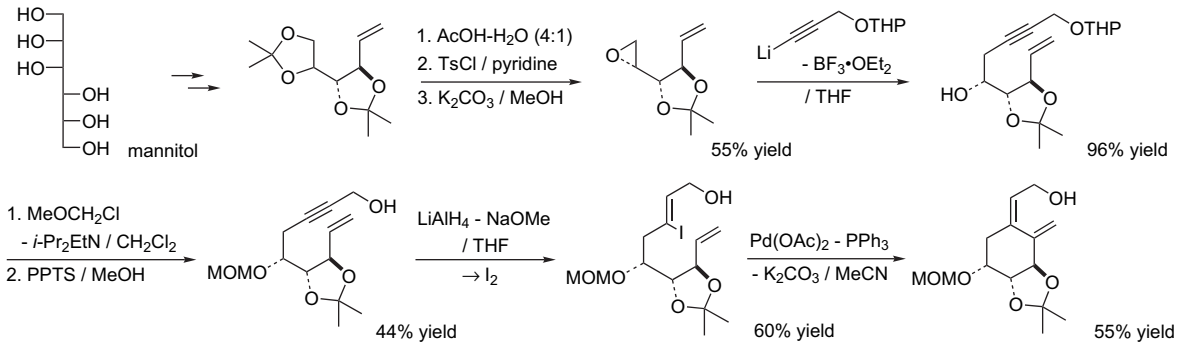
Scheme 196.



Scheme 197.

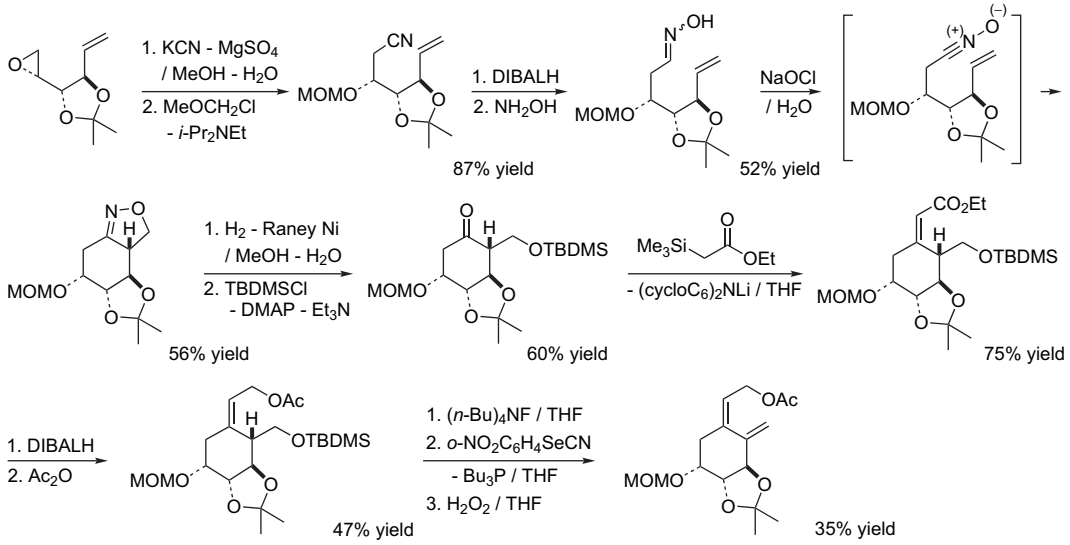
6.6. Use of mannitol

As shown previously, Takahashi and Nakazawa achieved the synthesis of the optically pure dienyl alcohol A-ring fragment for the preparation of 1α,2β,25-trihydroxyvitamin D_3 analogs. In this work, the requisite dihydroxylated monosubstituted epoxide was built up from the C_2 symmetric D-mannitol, as described in Scheme 198.[257]

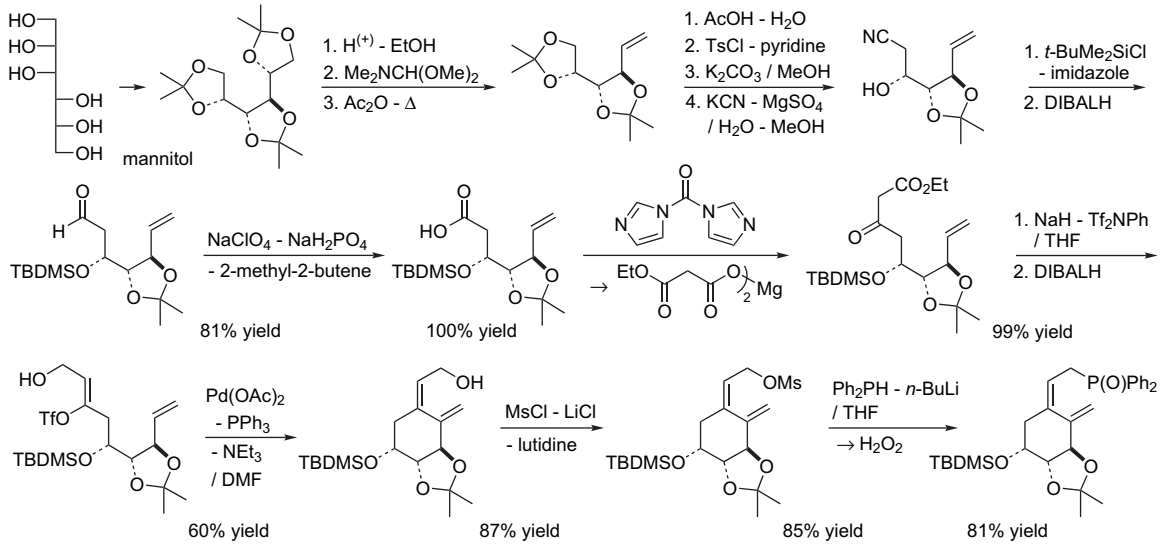


Scheme 198.

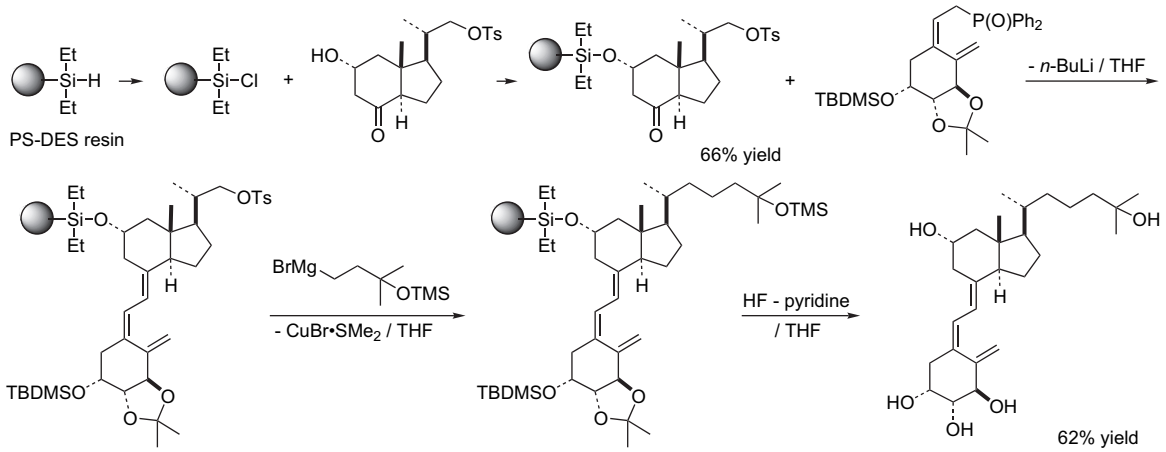
Ring opening of the latter epoxide with potassium cyanide yielded the corresponding terminal nitrile, which was exploited as a precursor of the 1α,2β,25-trihydroxyvitamin D_3 A-ring. From this building block, two strategies have been developed involving either a [3+2]-cycloaddition of a nitrile oxide and a Peterson-type reaction of a 2-alkoxymethylcyclohexanone (Scheme 199) or a β-keto ester formation and a palladium-catalyzed cyclization of a transient vinyl triflate (Scheme 200). An efficient solid-phase synthesis of vitamin D_3 analogs was also described considering the



Scheme 199.



Scheme 200.



Scheme 201.

coupling of the polymer-supported CD-ring with the A-ring allyl phosphine oxide and the subsequent alkylation of the resulting polymer-supported tosylate with the side chain Grignard reagent at C(21) (Scheme 201).[258]

Besides these efficient routes to A-ring synthons, a highly diastereoselective synthetic approach to the optically active 25-hydroxy Windaus–Grudmann ketone was proposed by Fukumoto and co-workers, in which the chirality was introduced by glyceraldehyde acetonide, readily available from D-mannitol. The *anti*-1,4-addition of an isoprenyl group to the (*R*)-isopropylideneglyceraldehyde-derived unsaturated ester,[259] the trans-*syn* selective intramolecular [4+2] cycloaddition reaction of an olefinic *ortho*-quinodimethane, and the complete regiocontrolled *trans*-hydrindane formation by intramolecular epoxide opening of a bis-sulfonyl epoxide represent the highlights of this synthesis (Scheme 202).[260]

Another glyceraldehyde acetonide-derived unsaturated ester was used to prepare (+)-11-deoxy-19-nor-corticosterone efficiently via a rather similar synthetic plan. The main steps that differed were the access to the intramolecular Diels–Alder cycloaddition precursor from the α-methylated unsaturated ester involving a Jonhson–Claisen rearrangement/benzocyclobutene alkylation sequence, the generation of the A-ring from the tricyclic adduct by a Birch reduction, reductive alkylation followed by Robinson annulation, and then various manipulations of the side chain. However, the Jonhson–Claisen rearrangement was carried out with poor yield and diastereoselectivity, as mentioned in Scheme 203.[261]

Mikami and co-workers showed that the (*S*)-(*Z*)-allylic alcohol obtained from (*R*)-glyceraldehyde acetonide and heated in the presence of the cyclic enol ether, 4,7-dimethoxy-1,2-dihydro-naphthalene, in a sealed tube at 180 °C, underwent a sequential Claisen rearrangement/intramolecular ene reaction to provide a seco-C steroid that cyclized to (+)-9(11)-dehydroestrone methyl ether through a modified McMurry coupling reaction (Scheme 204).[262] On the basis of this work, Groen-Piotrowska and Groen used an identical synthesis procedure to prepare norgestrel, but starting from the glyceraldehyde acetonide-derived ethyl ketone (Scheme 205).[263]

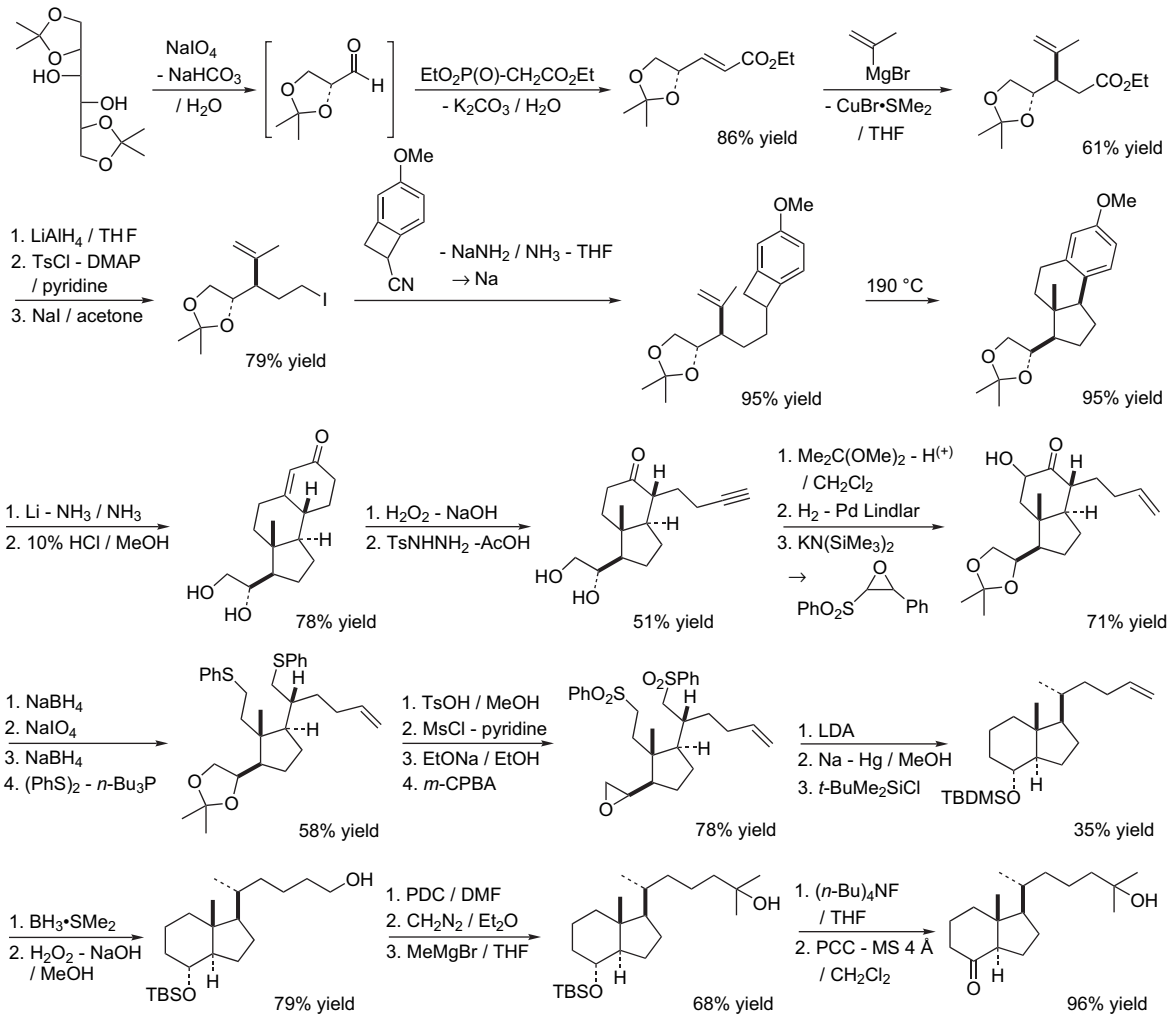
6.7. Use of xylose or arabinose

Aldopentoses such as xylose and arabinose could be used to prepare 1,7-enyne diols needed for the synthesis of 1α,25-dihydroxyvitamin D_3 and its trihydroxylated analog (ED-71). The latter analog involved Trost's approach implying a tandem palladium-catalyzed cross-coupling and intramolecular carbometallation between the acyclic enynes, prepared from D-xylose and D-arabinose, respectively, and the (*E*)-vinyl bromide of the Windaus–Grundmann ketone (Schemes 206 and 207).[264]

As observed before, introduction of a 2α-methyl or 2α-(3-hydroxypropyl) group into the 1α,25-dihydroxyvitamin D_3 native hormone increased significantly the binding activity to the VDR and the potency of calcium-mobilizing activity. In order to prepare a variety of 2α-substituted analogs, Takayama and co-workers opted for the Trost synthetic approach involving a tandem palladium-catalyzed cross-coupling and an intramolecular carbometallation between an acyclic enyne and the (*E*)-vinyl bromide of the Windaus–Grundmann ketone. The requisite enyne could be obtained from D-xylose after ring opening of the anomeric free hydroxyl carbohydrate by means of a Wittig reaction, terminal epoxide formation, and introduction of an acetylene unit into the epoxide using lithium acetylide. Elongation of the hydroxymethyl group was carried out in a conventional manner leading to a series of 2α-alkyl and 2α-hydroxyalkyl derivatives (Scheme 208).[265]

6.8. Use of glucose

Taking advantage of the convergent pallado-catalyzed strategy developed by Trost, Takayama and co-workers accomplished the synthesis of three novel 2α-(ω-hydroxyalkoxy)-1α,25-dihydroxyvitamin D_3 derivatives, the C(2)-α-modified A-ring precursors of which were elaborated stereoselectively starting from D-glucose. To construct these A-ring systems with the altrose configuration, the epoxide available from methyl α-D-glucoside was chosen as the chiral template and its regiospecific ring opening by a suitable alkanediol at the C(3)-position yielded the intermediate methyl 3-*O*-(3-hydroxyalkoxy)altropyranosides. Reduction of the related primary bromides with activated zinc liberated



Scheme 202.

the substituted 5-hexenols, readily transformed into olefinic epoxides. Introduction of the acetylene unit provided the desired 1,7-enyne (Scheme 209).[266] As mentioned by Kittaka, the 2α-substituents could be introduced by an addition reaction of Grignard reagent toward the sugar epoxide, easily obtained from D-glucose.[267] Following this strategy, new analogs of 1α,25-dihydroxyvitamin D_3, which possess a hydrophobic aromatic ring on the 2α position, have also been prepared.[268]

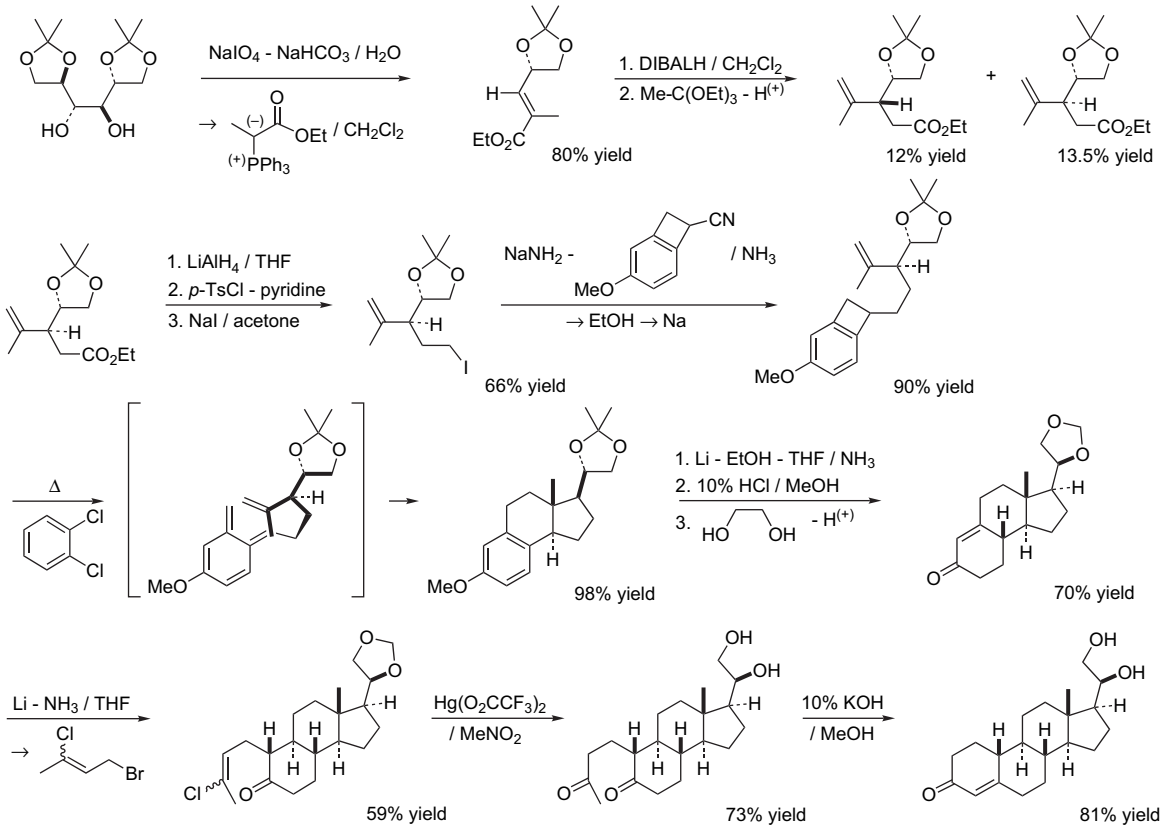
A sequence of two intramolecular Diels–Alder reactions was employed by Sherburn and co-workers as key steps for the construction of a 16-oxasteroid-type tetracyclic framework. The enantiomerically pure Diels–Alder precursor was prepared from D-glucose via a Wittig reaction between a known enal and the semistabilized ylide derived from 2,4-pentadienyltriphenylphosphonium bromide followed by condensation of the corresponding diene alcohol with a bis-dienophile acid (Scheme 210).[269]

6.9. Use of methyl lactate

Sato and co-workers showed that the reaction of the optically active propargyl phosphate prepared from methyl (*R*)-lactate in 98% ee with a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl generates a chiral allenyltitanium that can react with an alkylidenemalonate with an excellent regio- and *anti*-diastereoselectivity.[270] Further group transformations of the resultant Michael adduct, more particularly the δ-lactone formation and the *tert*-butyllithium-initiated iodoamide ring closure, led to the enantio-enriched (2*R*,3*R*)-2-methyl-3-[(1R)-1-methylprop-2-enyl]cyclopentanone. Robinson annulation with methyl vinyl ketone furnished the hydrindenone as a useful chiral building block for synthesizing vitamin D and steroid derivatives (Scheme 211).[271]

6.10. Use of pulegone

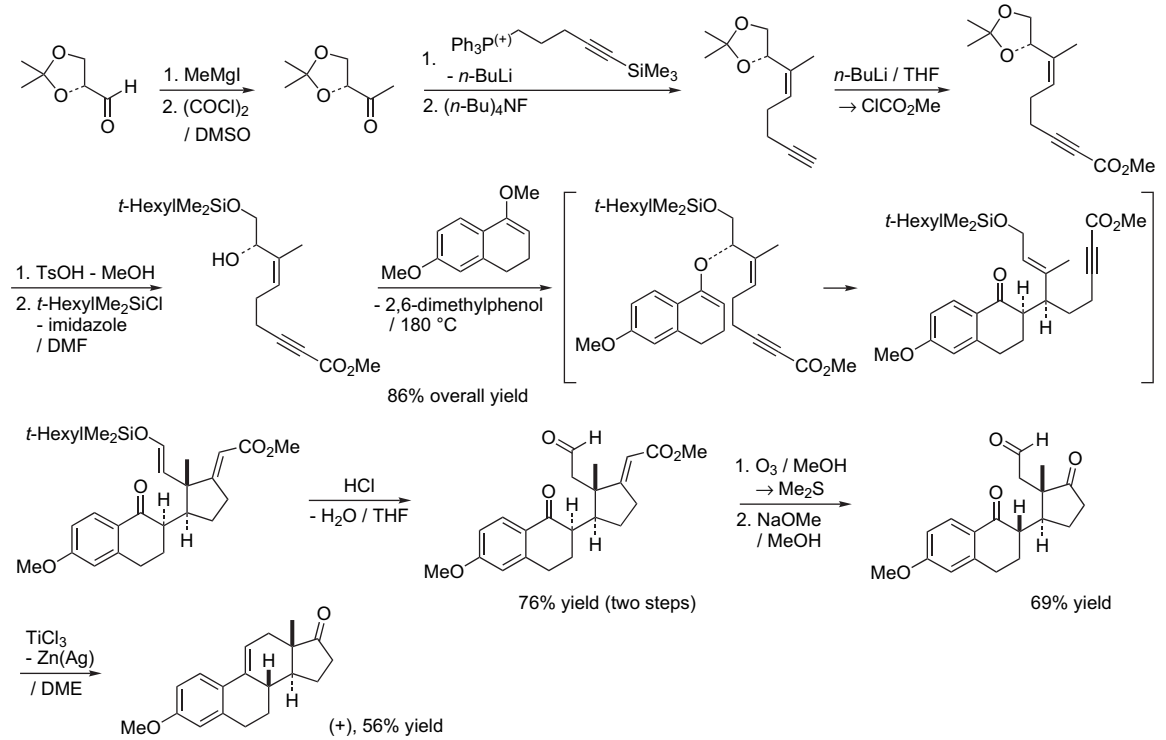
The intramolecular Diels–Alder (IMDA) reaction of a dienynylsulfone with a 5-6-fused bicyclic sulfone was exploited by Craig and co-workers to stereoselectively build the CD-ring fragment of vitamin D_3. The C(17) and C(20) stereocenters and the natural side chain in the IMDA substrate were installed by using (+)-(*R*)-citronellic acid, readily obtained from (+)-(*R*)-pulegone and Evan's oxazolidinone asymmetric alkylation methodology. The modest selectivity of the cyclization may be rationalized by considering the different $A_{1,3}$ strains in the competing transition-state conformations. Dihydrogenation of the cycloadduct gave the expected *trans*-hydrindane system. In parallel, it was demonstrated that IMDA reaction of the sulfonyl-substituted triene gave rise to the cis-ring junction compound (Scheme 212).[272]



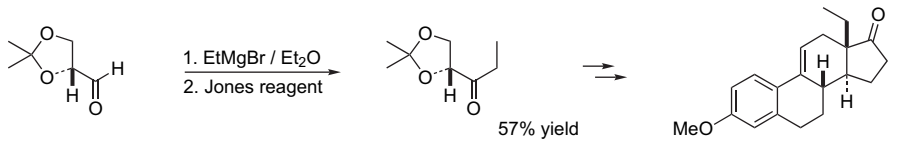
Scheme 203.

6.11. Use of ribonolactone

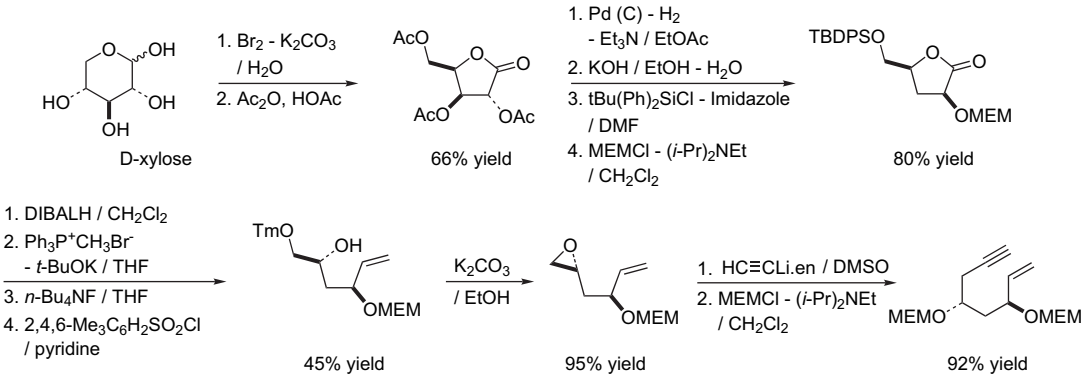
In 1985, Fukumoto and co-workers described an intramolecular cycloaddition of an olefinic *o*-quinodimethane for the construction of des-AB-aromatic steroids in optically active form, such as those found in (+)-aldosterone. Thermolysis of 4β-[2-(4-methoxybenzocyclobutenyl)ethyl]-5α-methoxymethyl-3-phenyl-thio-methylenefuran-2-ones, containing



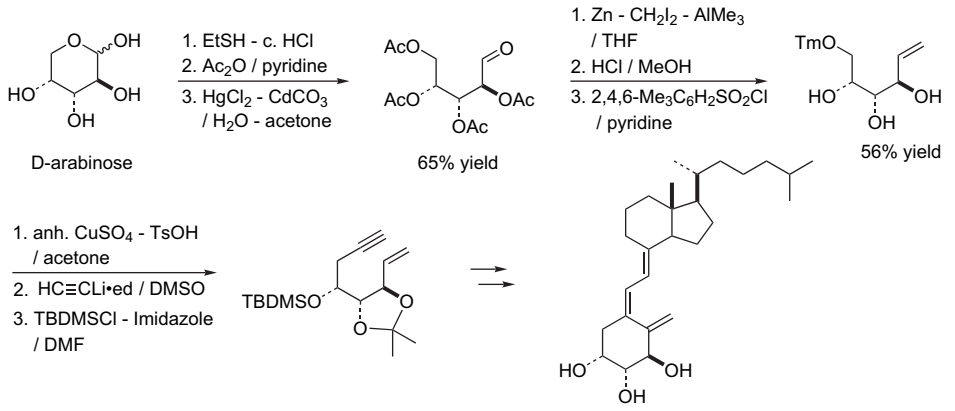
Scheme 204.



Scheme 205.



Scheme 206.



Scheme 207.

a butenolide ring conveniently prepared from D-(+)-ribonolactone,[273] yielded the tricyclic lactone as a mixture of trans/cis-ring junction isomers. The stereochemical outcome of the reaction is related to the nature of the R group and was shown to be controlled in the transition state by the steric repulsion between the *o*-quinodimethane moiety and the bulky R group (Scheme 213).[274]

6.12. Use of glutamic acid

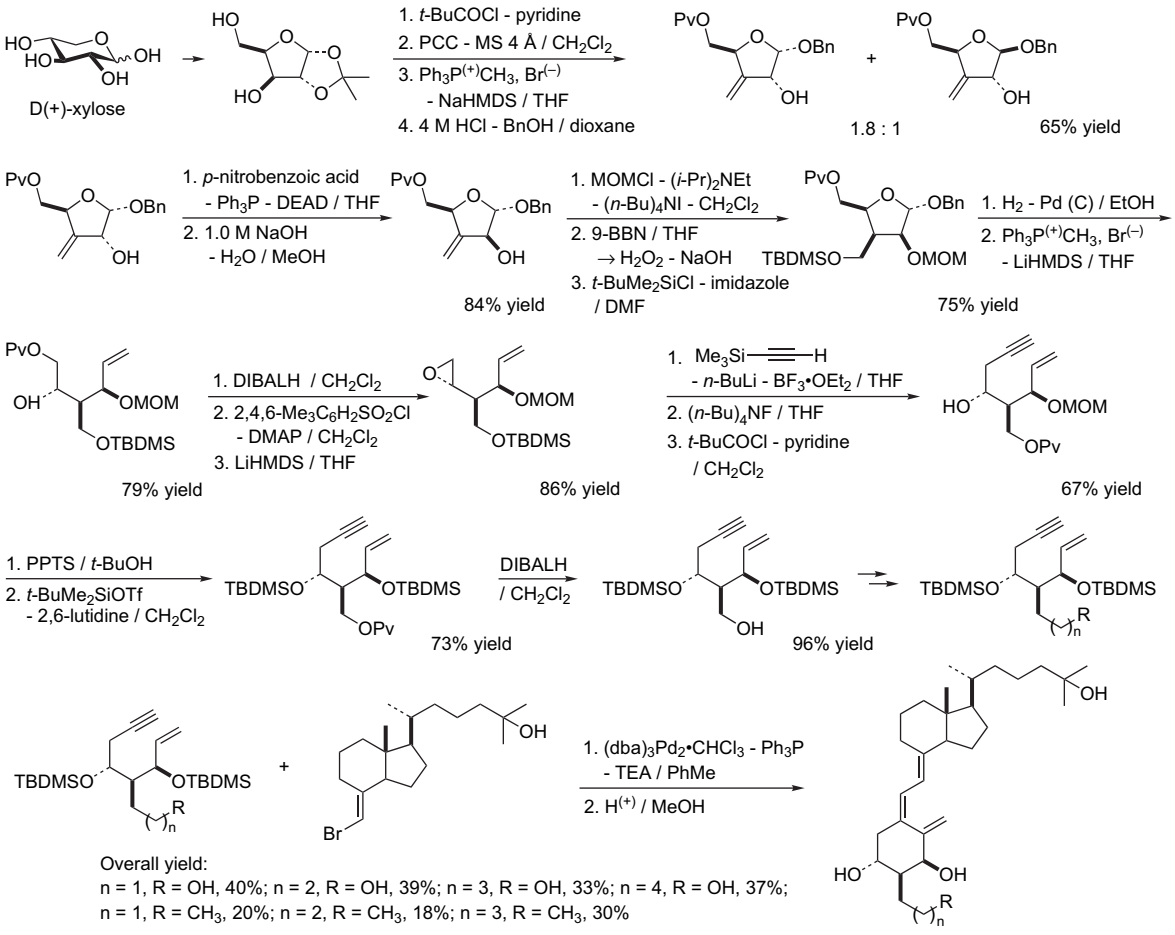
(*S*)-γ-Trityloxymethyl-γ-butyrolactone, obtained in four steps from L-glutamic acid, was used by Takano's group in the preparation of a useful chiral building block disubstituted cyclopentanone for the synthesis of vitamin D_3 metabolites that possess the common C(17*R*) and C(20*R*) configurations. The starting lactone was subjected to aldol condensation with 2-methyl-2-heptene-2-one. Then, the bulkiness of the trityloxymethyl group at the γ-position was exploited to introduce the chirality at C(17) and C(20) via stereoselective hydrogenation of the unsaturated lactone and kinetic protonation of its lithium enolate. Finally, Dieckmann condensation of an advanced acyclic intermediate and subsequent decarboxylation liberated the cyclopentanone (Scheme 214).[275]

6.13. Use of limonene

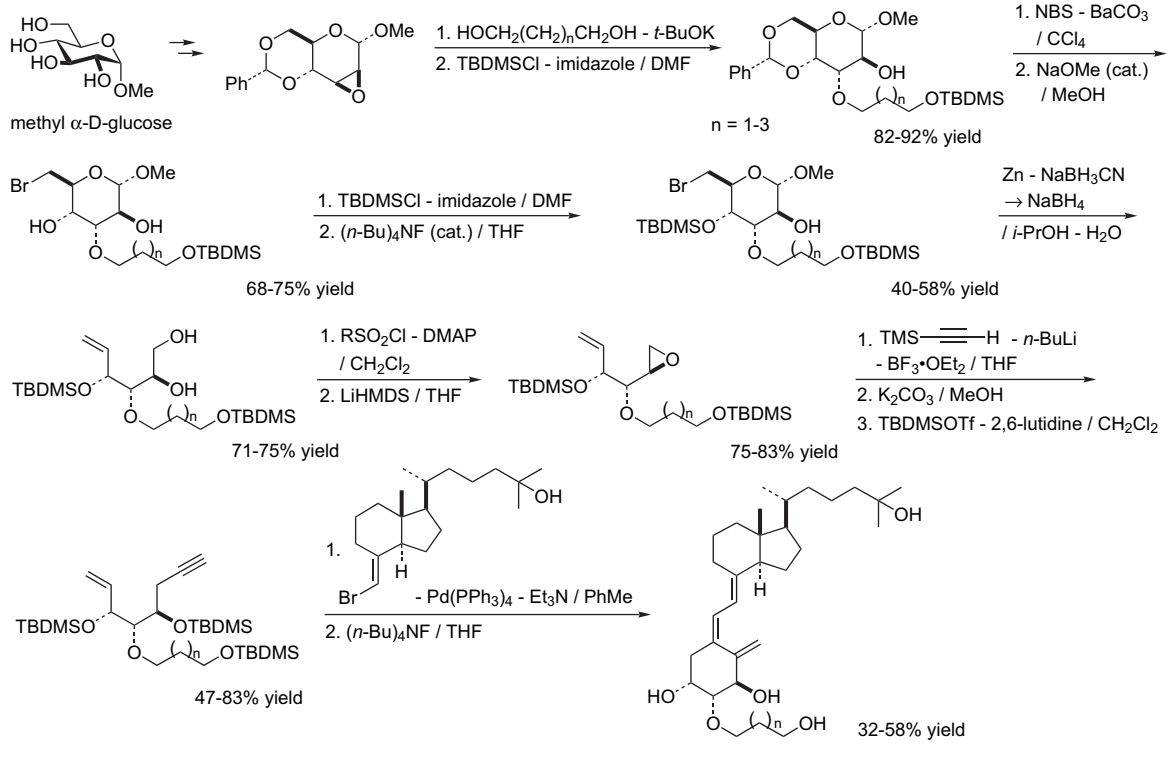
A new C(19) hydroxylated enyne, as a potential A-ring building block of vitamin D analogs, was synthesized in enantiomerically pure form in nine steps from (−)-(*S*)-limonene by Santelli and co-workers. Their concise approach involved ozonolysis of 1,2-limonene oxide followed by a Criegee rearrangement, epoxide *trans*-diaxial ring opening by lithium acetylide, elimination, epoxidation, and *syn* β-elimination of the resulting homopropargylic oxirane (Scheme 215).[276]

6.14. Use of α-thujone

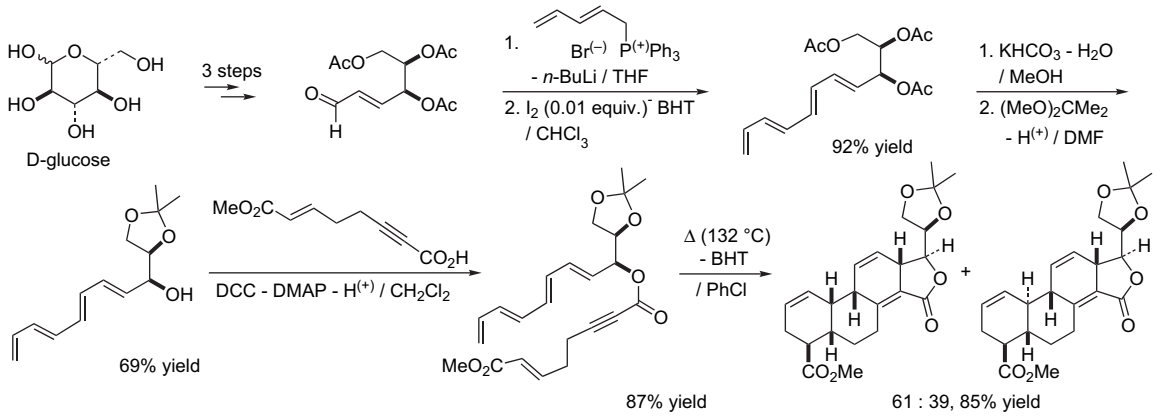
In 1982, Kutney and co-workers reported a one-step synthesis of an optically active steroidal analog from a thujone-derived tricyclic enone. Treatment of the enone with an



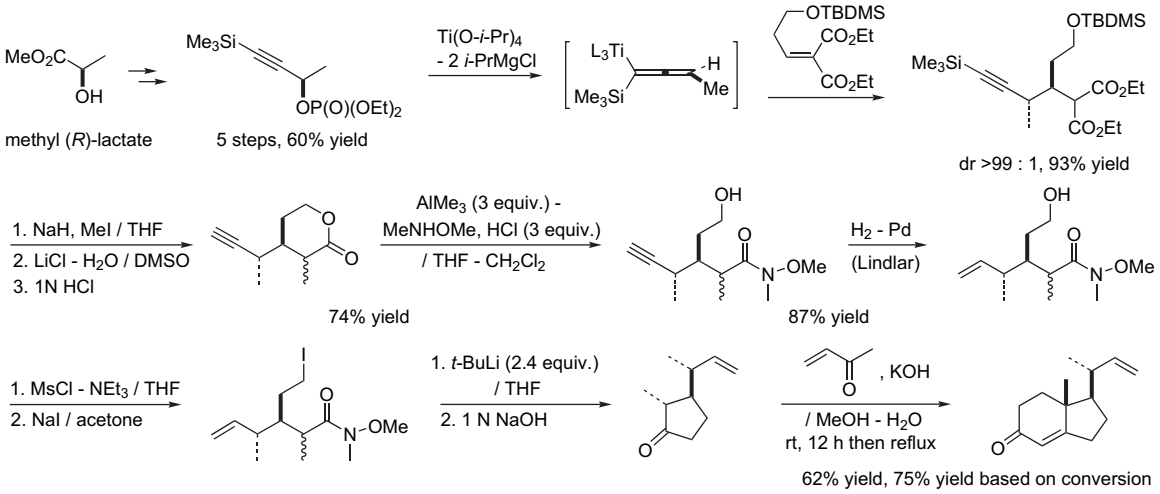
Scheme 208.



Scheme 209.



Scheme 210.



Scheme 211.

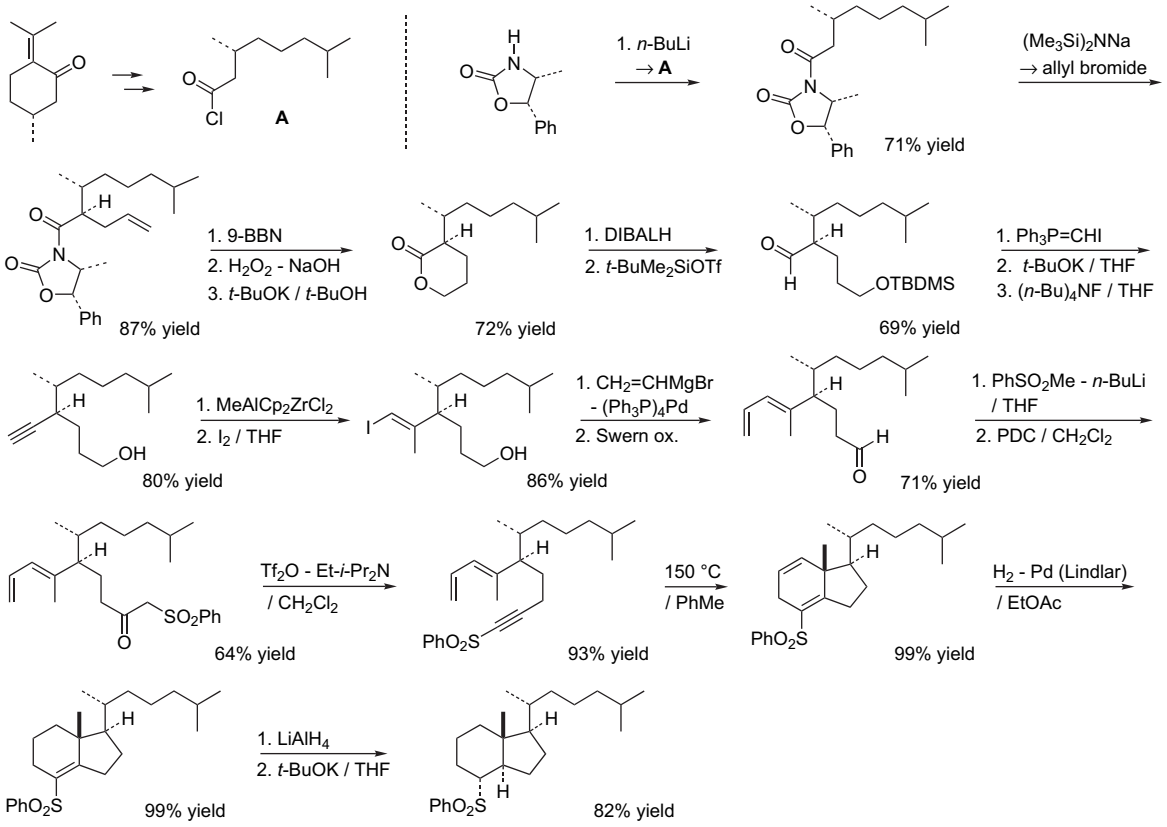
equivalent reagent of ethyl vinyl ketone yielded the classic Robinson annulation adduct in 33% yield together with the unexpected pentacyclic compound isolated in 39% yield. Its formation may involve cyclocondensation of the triketone intermediate resulting from the addition of two molecules of ethyl vinyl ketone to the enone and subsequent dehydration. One year later, the same authors applied the Fujimoto–Belleau reaction[32] to transform the dienol lactone obtained from the thujone-derived enone into an α-substituted dienone. Conventional Birch reductive alkylation, hydrolysis of the acetal, and base-promoted cyclization gave the desired steroid analog with a CD cis junction (Scheme 216).[277]

6.15. Use of epichlorhydrin

An enantioconvergent approach to the linear and cyclic A-ring precursors of calcitriol from either (*R*)- or (*S*)-epichlorhydrin was proposed by Tazumi and Ogasawara. Sequential reaction with prop-1-ynyl tetrahydropyranyl ether and trimethylsilylacetylene and vice versa generated a common diynol, which was transformed to Trost's enynol. From this latter compound, the corresponding ethyl propiolate underwent a palladium(0)-catalyzed cycloisomerization reaction to give the dialkylidenecyclohexane as a known A-ring precursor (Scheme 217).[278] Concomitantly, a similar route to Hoffmann-La Roche's A-ring synthon, developed by Hatakeyama and co-workers, centered on a double propargylation of (*R*)-epichlorhydrin, a diastereoselective epoxidation of the (*E*)-allyl alcohol unit and a palladium-(0)-promoted intramolecular Heck-type reaction of an ω-vinyl-(*Z*)-iodoalkene obtained by reductive iodination of a propargylic alcohol fragment (Scheme 218).[279]

An efficient access to the enantiopure 5-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone was proposed by Sato and Kasatkin. The reaction sequence outlined in Scheme 219 included a Kulinkovich-type hydroxycyclopropanation reaction[280] of ethyl 3-hydrohex-5-enoate, consisting of an intramolecular nucleophilic acyl substitution mediated by Ti(O-*i*-Pr)$_4$/2*i*-PrMgBr, and an $FeCl_3$-assisted ring expansion in the next step. The non-racemic starting β-hydroxy ester was elaborated from the commercially available (*S*)-epichlorhydrin[281] or the ethyl 4-chloro-3-hydroxybutyrate easily obtained by enzymatic reduction of the corresponding β-keto ester with *Saccharomyces cerevisiae*.[282]

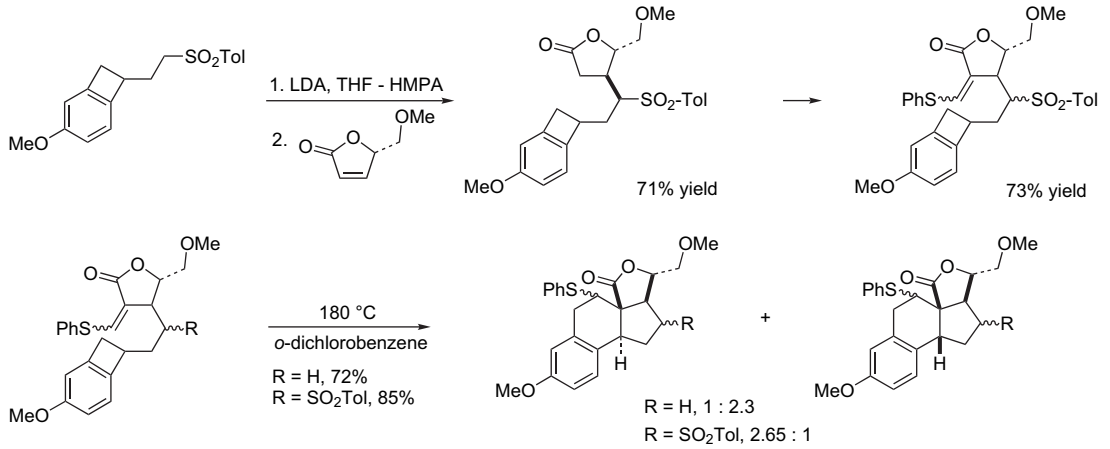
This building block could be rapidly modified to an A-ring synthon of 1α,25-dihydroxyvitamin D_3 according to two different synthetic routes from a common intermediate, obtained by a diastereoselective cat. OsO_4/NMO



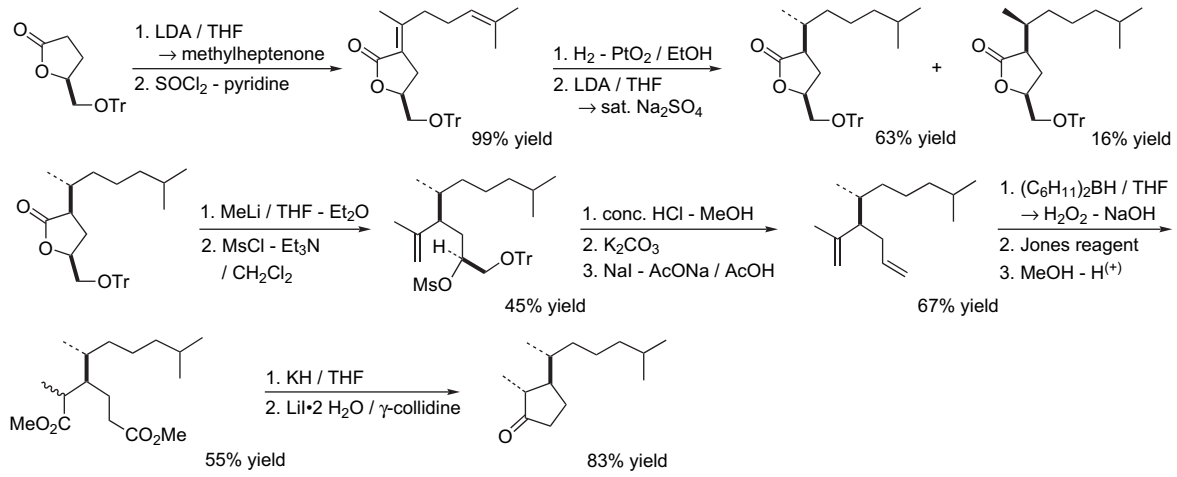
Scheme 212.

dihydroxylation (which set the stereochemistry of the hydroxyl group at C(1)), a Reformatsky reaction, a regioselective protection of the hydroxyl group at C(1), and a Swern oxidation at C(10). The methylenation reaction of the ketone with the Zn-CH_2Br_2/$TiCl_4$ reagent and the β-elimination of the tertiary alcohol, achieved by treatment with Et_2NH and cat. $Pd(PPh_3)_4$, liberated the (*E*)-α,β-unsaturated ester, which could be converted into the (*Z*)-isomer by photoisomerization (Scheme 220).[283] The latter isomer was also accessible by $Sc(OTf)_3$-catalyzed intramolecular lactonization in acetic anhydride and β-elimination of the acetate group that fixed the (*Z*)-geometry of the trisubstituted double bond (Scheme 221).[284]

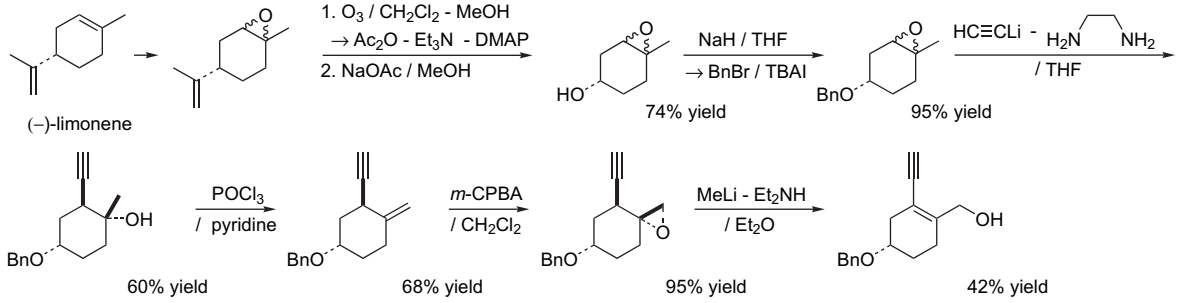
From the previous optically pure silyl-protected 5-hydroxy-2-cyclohexenone, Sato and co-workers reported an efficient synthesis of the A-ring precursor of 19-nor-1α,25-dihydroxyvitamin D_3 and its ^{13}C- or ^{2}H-labeled derivatives. These syntheses centered on a practical five-step reaction sequence, which comprised a highly diastereoselective epoxidation, a Horner–Wadsworth–Emmons olefination with either $(EtO)_2(O)PCH_2CO_2Et$ or $(EtO)_2(O)P–^{13}CH_2CO_2Et$ and a regiospecific reductive ring opening of the epoxide carried out with HCO_2H or DCO_2D in the presence of $Pd_2(dba)_3$–$CHCl_3$/Bu_3P.[285] By another route, the epoxy ketone underwent a stereospecific Wittig olefination with $(Ph_3P^{(+)}CH_2Br)Br^{(-)}$ and KHMDS followed by an epoxide



Scheme 213.



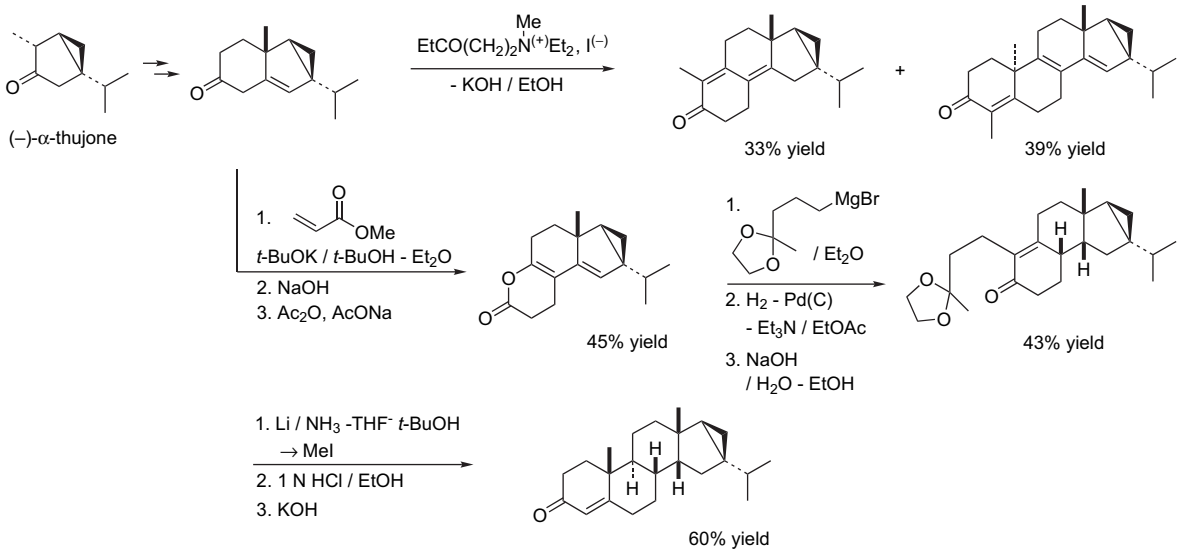
Scheme 214.



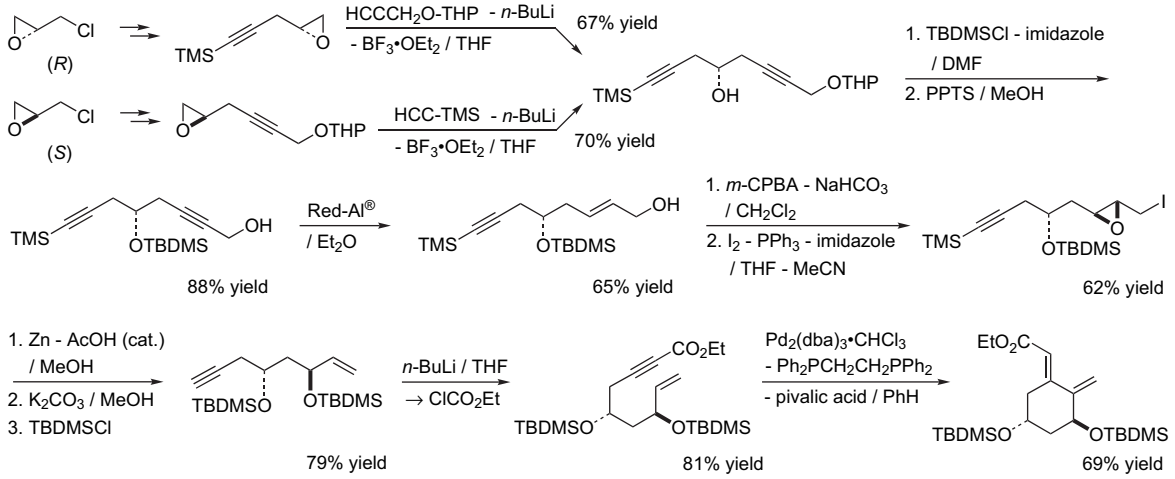
Scheme 215.

ring opening of the diene monoepoxide by reduction with DIBALH and conversion of the vinyl bromide moiety into vinyl boronate through a sequential treatment with *t*-BuLi, $B(O\text{-}i\text{-}Pr)_3$, aqueous NH_4Cl, and pinacol. Thus, the latter boronate was subjected to a Suzuki–Miyaura coupling reaction with the bromide compound of the CD-ring portion (Scheme 222). Similarly, cross-coupling with the A-ring bromide and the CD-ring boronate proceeded in reasonable yield and this methodology was immediately applied to the solid-phase synthesis of des-CD-19-nor-vitamin D_3 derivatives (Scheme 223).[286]

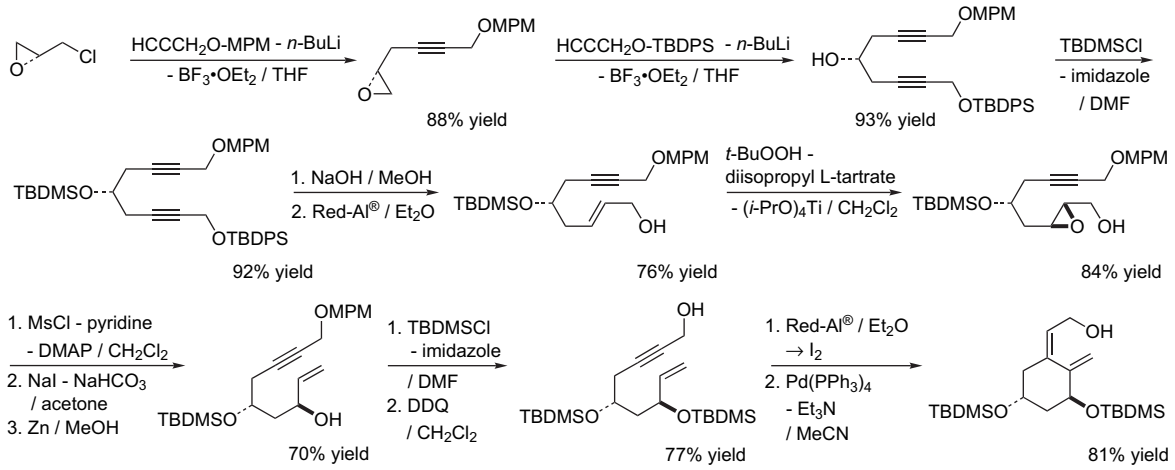
A strategy for the solid-phase synthesis of a vitamin D_3 library was developed by Takahashi. The modified CD-rings and the side chain moieties were readily available from the Inhoffen–Lythgoe diol and bromo esters, respectively, and



Scheme 216.



Scheme 217.

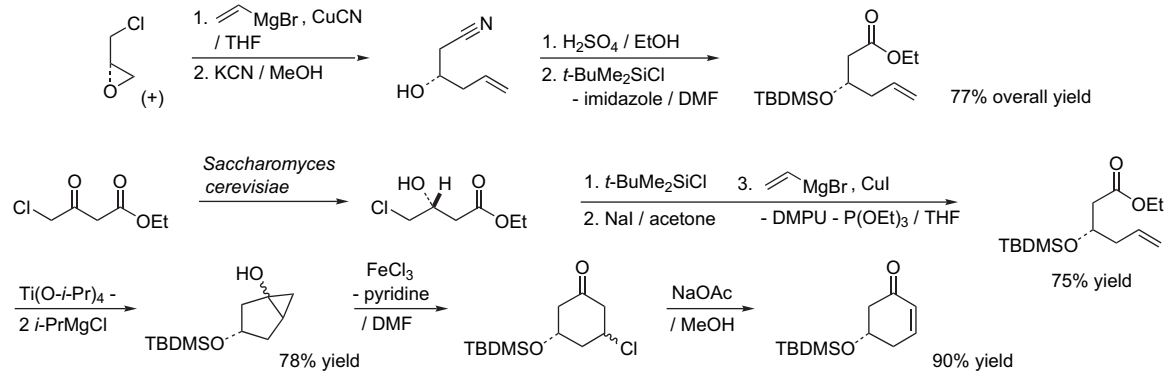


Scheme 218.

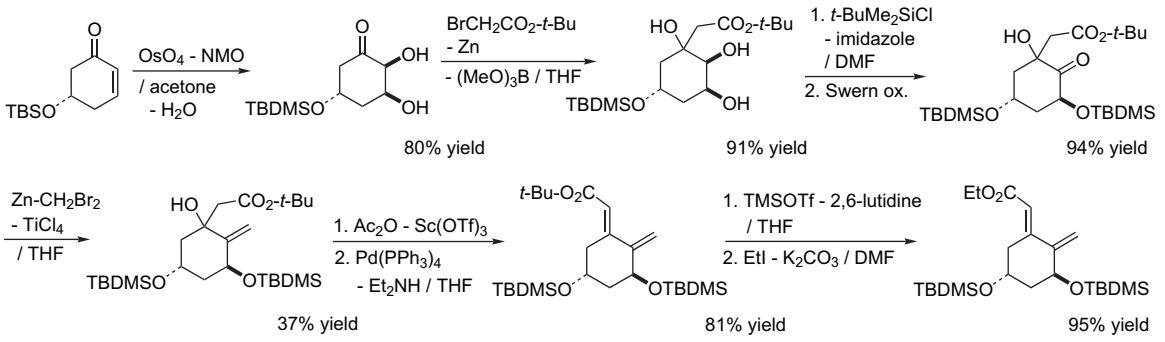
the A-ring moieties could be prepared from the corresponding enol triflates through a Pd(0)-catalyzed intramolecular Heck reaction. The enol triflates were accessible by diastereoselective reduction of enantiomerically pure β-hydroxyketones, prepared by chemoselective alkylation of the lithiated protected cyanohydrin of acrolein with (*R*)- or (*S*)-epichlorohydrin (Scheme 224).[287]

6.16. Use of methyl 3-hydroxy-2-methylpropionate

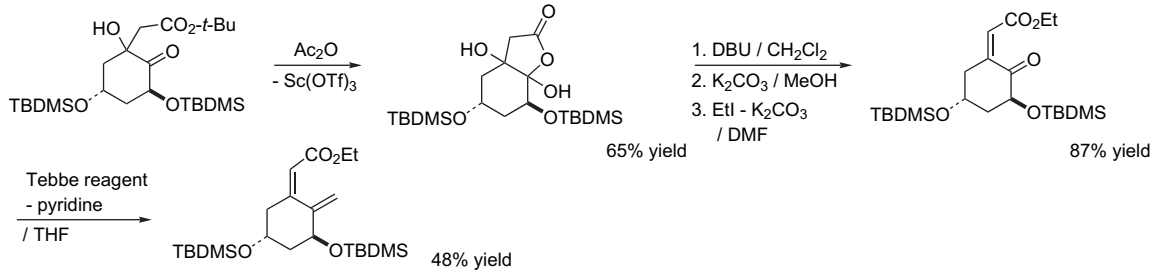
Grieco and co-workers achieved a formal synthesis of the Inhoffen–Lythgoe diol employing a key diastereoselective intermolecular aqueous Diels–Alder strategy, in which the C(20) stereocenter was part of the diene unit that was used to elaborate the C(13) and C(17) stereocenters of



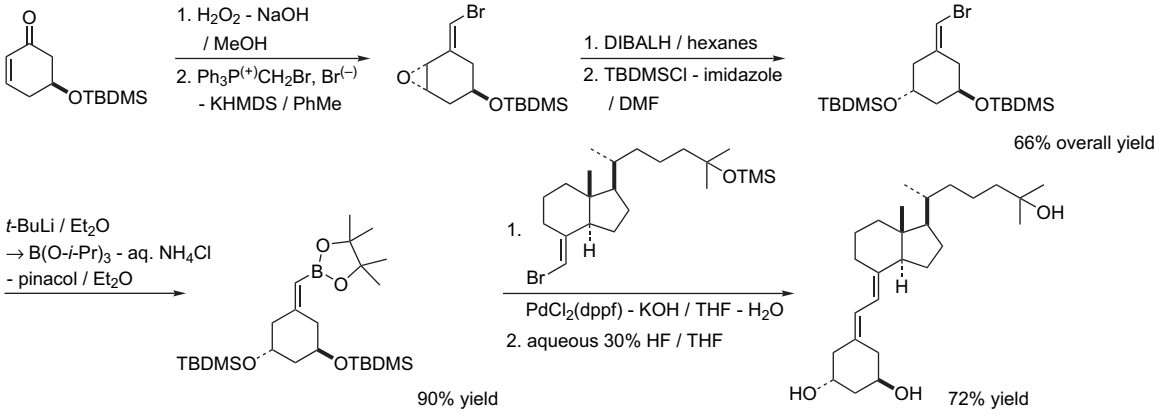
Scheme 219.



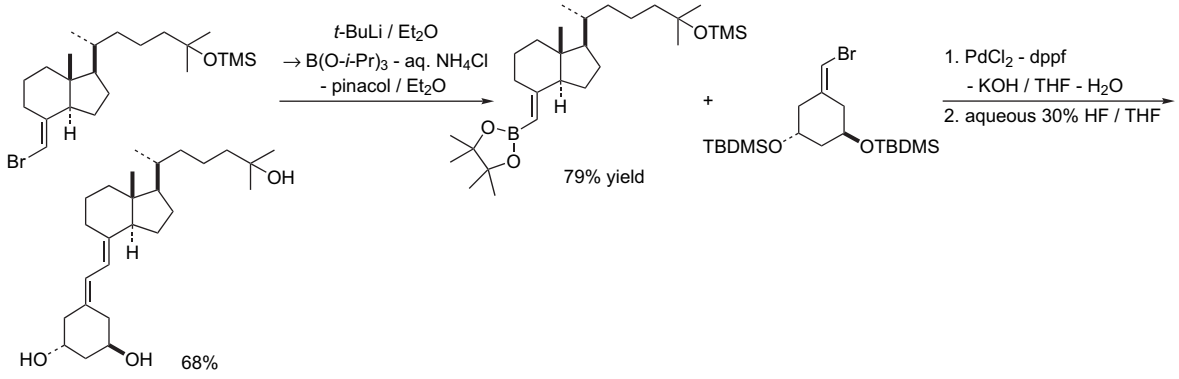
Scheme 220.



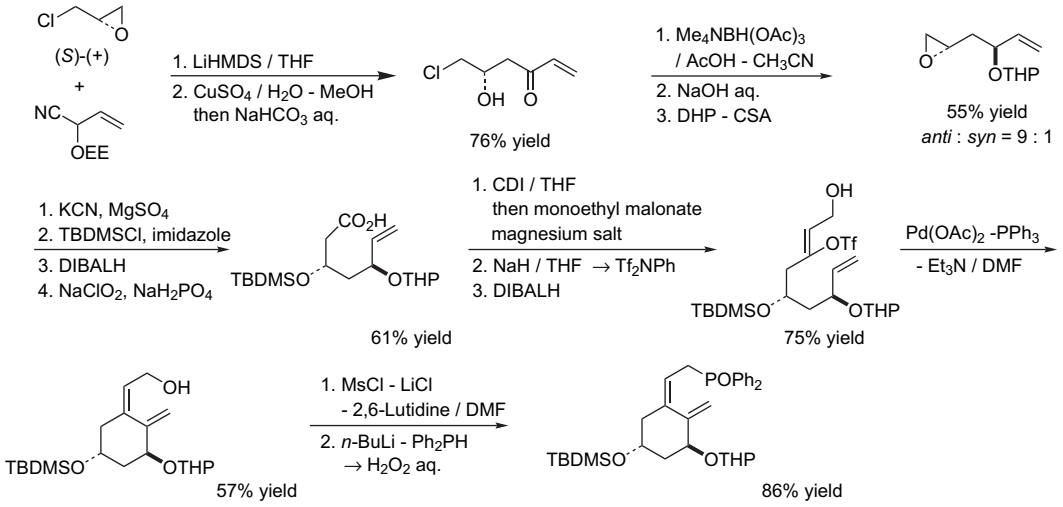
Scheme 221.



Scheme 222.



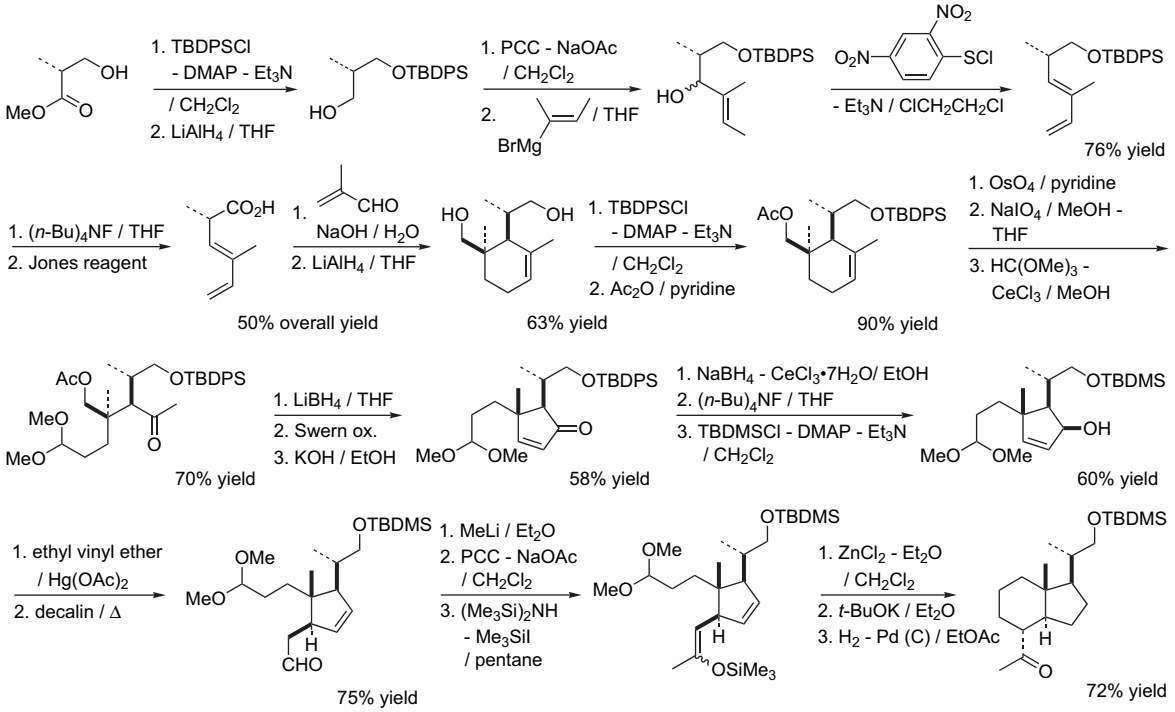
Scheme 223.



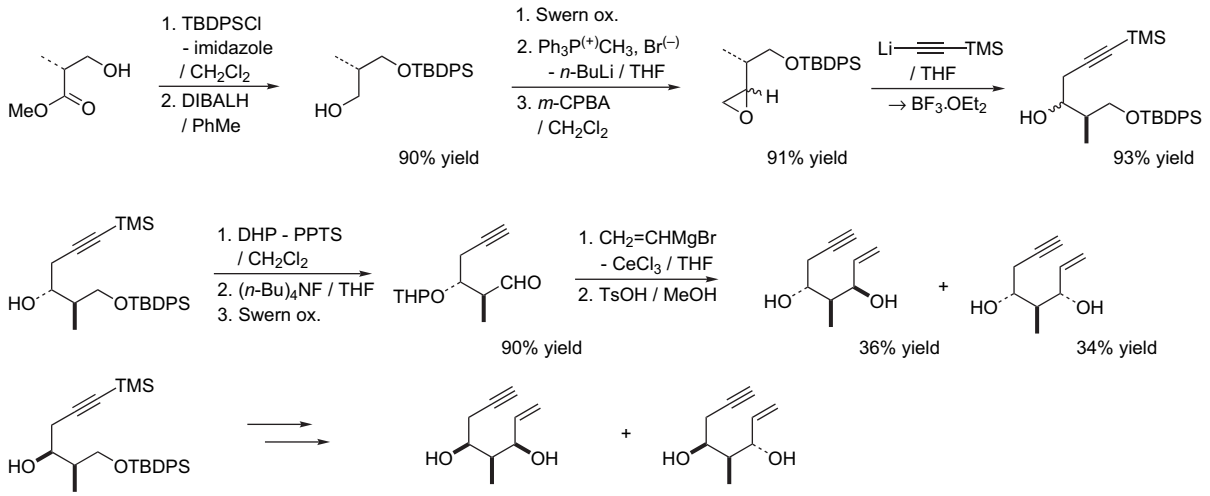
Scheme 224.

the latent CD *trans*-fused hydrindane ring system. The sodium salt of the chiral diene acid, which served as a partner in the Diels–Alder process with methacrolein, was accessible in a few steps from (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate using a tandem sulfenate–sulfoxide [2,3] sigmatropic rearrangement/*syn* elimination strategy. Subsequent oxidative cleavage of the bisprotected diol and aldol condensation provided the D-ring precursor cyclopentenone, which was diastereoselectively reduced into the desired alcohol. Chirality transfer from C(16) to C(14) proceeded via a Claisen rearrangement and yielded the γ,δ-unsaturated aldehyde. The thermodynamic silyl enol ether of the related methyl ketone was then subjected to a zinc chloride-induced aldol condensation and final reduction of the diene unit generated the *trans*-fused hydrindane (Scheme 225).[288]

The use of both enantiomers of methyl 3-hydroxy-2-methylpropionate, as starting materials, allowed the synthesis of A-ring diastereoisomers of 2-methyl-1,25-dihydroxyvitamin D_3 and their 20-epimers. Takayama and co-workers have developed a versatile method for preparing a wide range of 2-methyl-substituted A-ring enyne synthons, based on the introduction of an acetylene unit and a vinyl group into an epoxy aldehyde precursor derived from methyl 3-hydroxy-2-methylpropionate. Coupling of the resulting A-ring enynes with the CD-ring portions in the presence of the Pd catalyst furnished the 2-methyl analogs (Scheme 226).[289]



Scheme 225.



Scheme 226.

6.17. Use of α-pinene

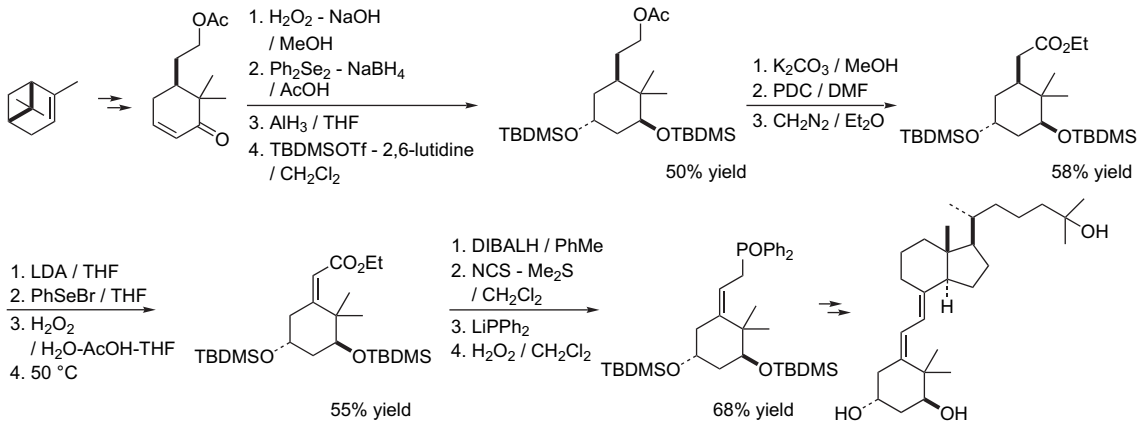
Linclau and Vandewalle have reported a synthesis of 10,19-dihydro-10-methyl 1α,25-dihydroxyvitamin D_3 by developing a 10,10-dimethyl-substituted novel A-ring phosphine oxide precursor, the formation of which was based on the selective functionalization of an advanced intermediate cyclohexenone derived from (+)-α-pinene. The crucial steps involved the elaboration of the 1,3-trans diol configuration via a selective epoxidation of the enone motif and the formation of the *Z*-unsaturated ester by a highly selective phenylselenylation–oxidation–elimination procedure (Scheme 227).[290]

6.18. Use of β-pinene

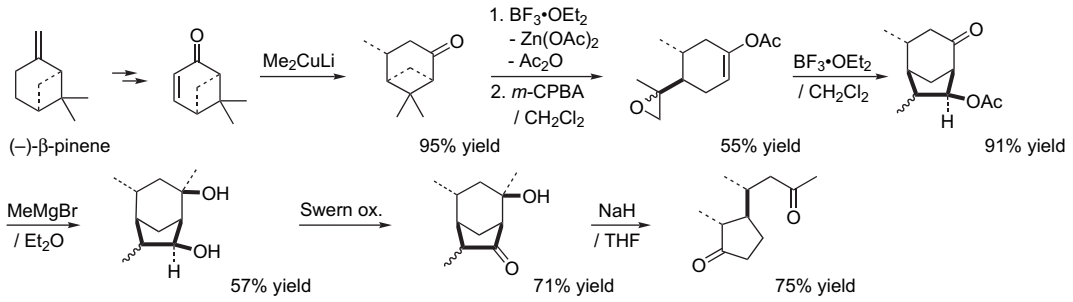
An enantioselective approach to cyclopentanoids such as steroid D-ring synthons possessing a functionalized side chain was proposed by Kato and co-workers. They first showed that $BF_3 \cdot Et_2O$-promoted cyclobutane ring opening of (1*R*,4*R*,5*R*)-4-methylnopinone, readily obtained from (−)-β-pinene by ozonolysis and conjugate addition of lithium dimethylcuprate, gave the enol acetate. The epoxidation adducts underwent a Lewis acid-induced tandem epoxide rearrangement/intramolecular aldol-type condensation and a few chemical transformations afforded the bicyclo-[3.2.1]octan-2-ones. A smooth retro-aldol condensation followed by isomerization of the ring methyl group liberated the substituted cyclopentanone including both the secondary methyl group (*R*) in the side chain and the side chain itself (*R*) with the same absolute configuration of steroidal substrates (Scheme 228).[291]

6.19. Use of menthol

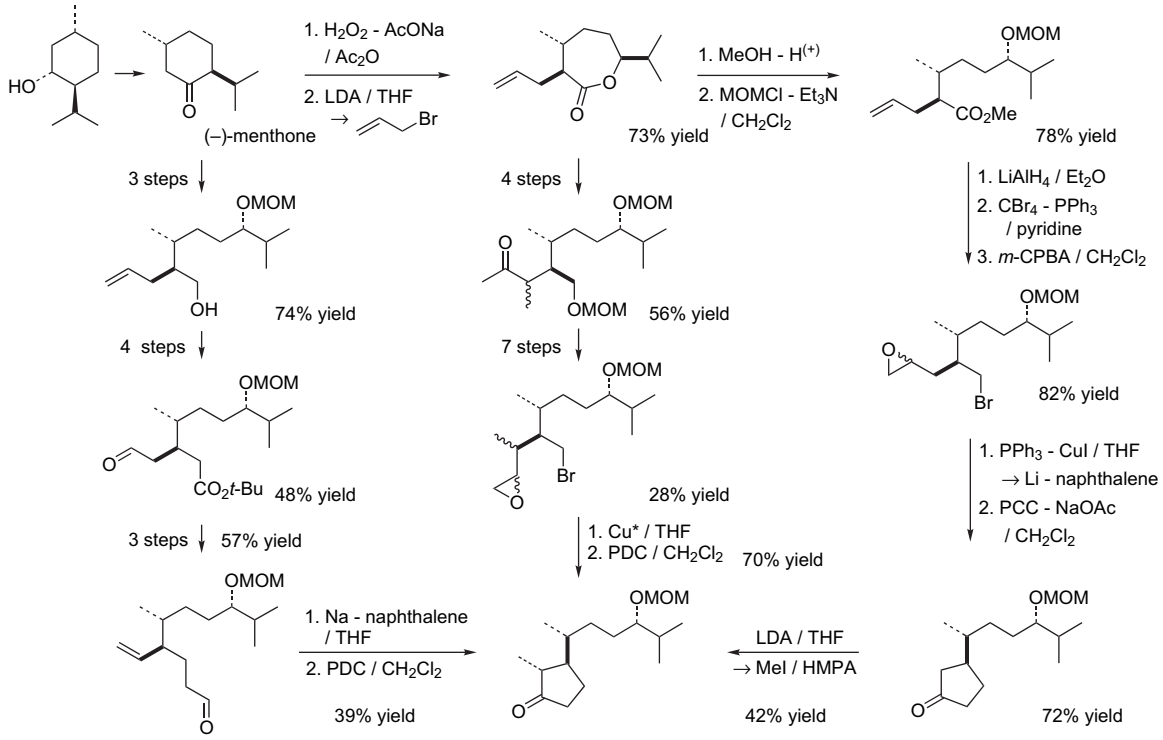
In 1992, Daniewski and Warchol provided a construction of the D-ring building block of (24*S*)-24-hydroxy vitamin D_3 from natural (−)-menthol. The terpene was successively oxidized to (−)-menthone and the corresponding lactone, which was alkylated with allyl bromide to a single allyl derivative having substitutents at trans positions to the methyl group. This latter allyl compound was transformed into the desired cyclopentanone according to three different routes, as described in Scheme 229. The two bromo epoxide intermediates cyclized by treatment with active copper, whereas the enaldehyde underwent a free-radical cyclization in the presence of Na/naphthalene.[292] A Taber cyclization of a (−)-menthol-derived diazo-β-keto ester catalyzed by rhodium diacetate was also utilized for the synthesis of the D segment (Scheme 230).[293]



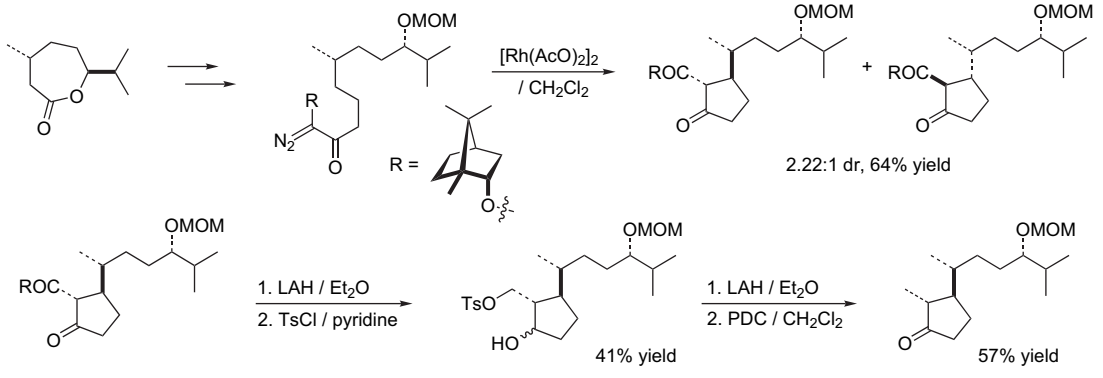
Scheme 227.



Scheme 228.



Scheme 229.



Scheme 230.

7. Use of enzymes

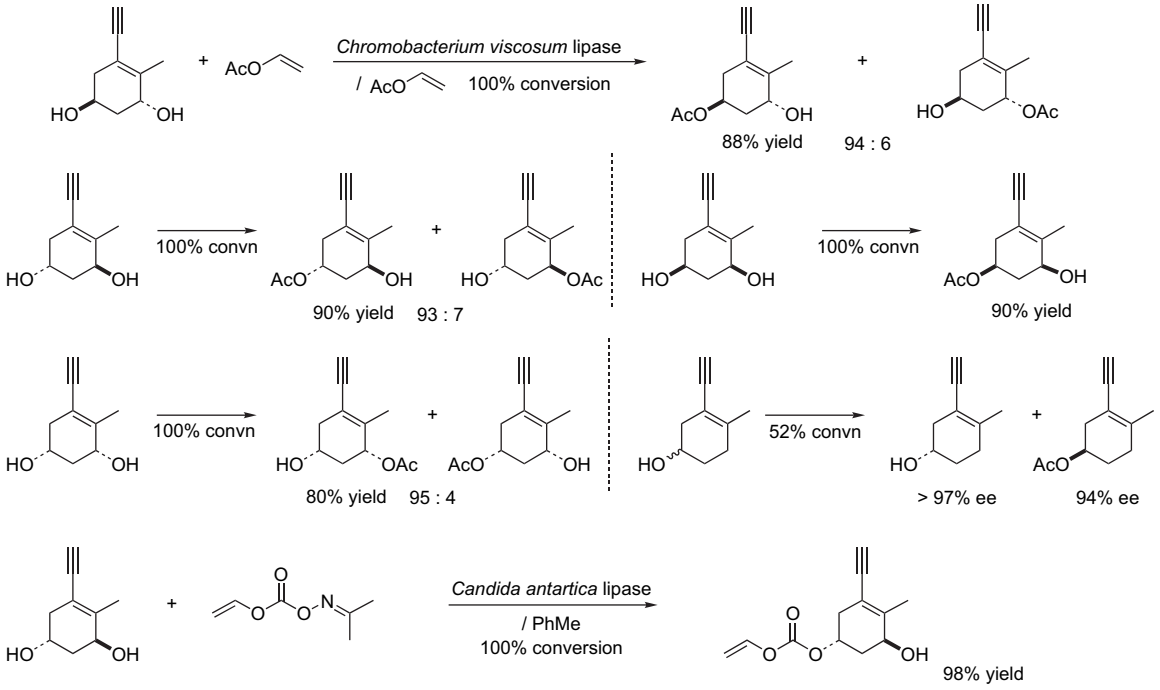
An alternative approach to the synthesis of enantiopure vitamin D A-ring precursors that does not require the use of molecules from the chiral pool was proposed by Okamura and co-workers. This latter method consisted of a kinetic enzymatic resolution of the known racemic enynol, which involved *Chromobacterium viscosum* lipase (CVL)-catalyzed acylation of one enantiomer with vinyl acetate and led to the (*R*)-(+)-acetate and the unchanged (*S*)-(−)-alcohol

isolated in 94% yield and >97% ee, respectively. Moreover, related enyne diols were regioselectively acylated either at the allylic C(1) hydroxyl for the (*R*,*R*) cis derivative or at the nonallylic C(3)-position for the other stereoisomers.[294a] CVL proved to be the most efficient enzyme for acylation reactions, while *Candida antarctica* lipase (CAL) was found to be the best for enzymatic synthesis of carbonates with (vinyloxy)-carbonyl oxime. Similarly, the alkoxycarbonylation occurred preferentially at the allylic C(1) hydroxyl for the (*R*,*R*) cis derivative or at C-3 for the other stereoisomers. In addition, the resulting carbonates could be efficiently converted into carbamates by reaction with amino derivatives.[294b,c] Finally, CAL-B or CVL catalyzed the alkoxycarbonylation process of 19-nor-A-ring stereoisomers of 1α,25-dihydroxy-19-nor-previtamin D_3 in the presence of acetone *O*-(phenoxycarbonyl)-oxime with high selectivity. The opposite regioselectivity shown by each couple of enantiomers is noteworthy (Scheme 231).[294d,295] Regioselective enzymatic hydrolysis reactions of dicarbonate A-ring stereoisomeric precursors with *Candida rugosa* lipase (CRL) and CVL have also been accomplished.[296]

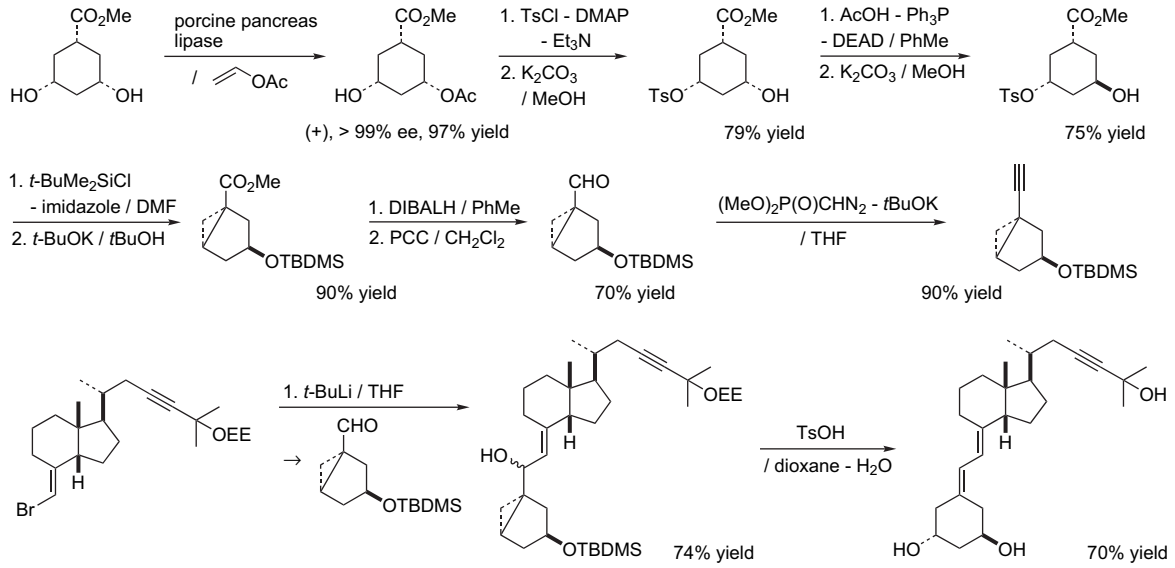
Enzymatic desymmetrization of *meso* all-*cis*-3,5-dihydroxy-1-(methoxycarbonyl) cyclohexane into a single enantiomer provided an elegant route to the synthesis of A-ring synthons of 19-nor vitamin D analogs. Porcine pancreas lipase (PPL)-catalyzed transesterification of the 1,3-cyclohexanediol-type compound with vinyl acetate was developed by Vandewalle and co-workers to prepare enantiopure intermediates of (1*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)bicyclo[3.1.0]hexane-1-carbaldehyde and its diastereoisomers.[297] The resulting monoacetate alcohol was subsequently tosylated and submitted to an intramolecular alkylation of the enolate ester followed by a two-step reduction–oxidation procedure to furnish the bicyclic aldehyde. Cross-coupling with the vinylic lithium derivative of appropriate *cis*-fused hydrindanes and acid-promoted carbinol ring opening produced the 14-*epi*-19-nor-1α,25-dihydroxyvitamin D_3 analogs (Scheme 232).[298]

In parallel studies, Kalkote and co-workers have accomplished the desymmetrization of the *cis*-triacetate derivative of phloroglucitol through selective enzymatic hydrolysis of two different acetate groups with porcine liver esterase. An inversion of the alcohol under Mitsunobu conditions was performed on the mixed THP and TBDMS bisprotected triol, generating, at this point, a common precursor of both enantiomeric forms of the bisprotected *trans*-3,5-dihydroxy cyclohexanone[299] utilized in the synthesis of 19-nor, des-CD vitamin D_3 analogs by Hilpert and Wirz (Scheme 233).[300]

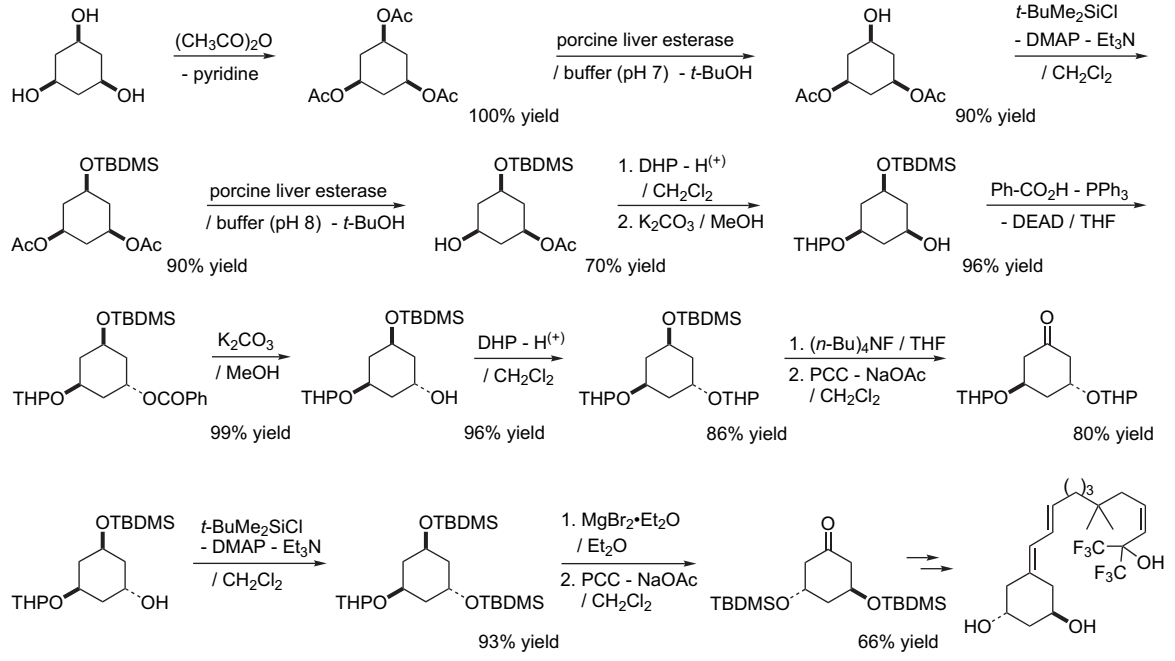
As already shown, enantiopure (3*S*,5*R*)-oct-1-en-7-yne-3,5-diol derivatives were considered as useful intermediates for A-ring fragment synthesis required in the preparation of 1α,25-dihydroxyvitamin D_3 and analogs involving either palladium-catalyzed alkylative enyne cyclization developed by Trost or Lythgoe's coupling between the corresponding phosphine oxide and Windaus–Grundmann ketone. The construction of the 1,7-enynes started with a kinetic resolution of the racemic β-hydroxy ester, resulting from the aldol reaction of acrolein with the lithium enolate of *tert*-butyl acetate, via lipase-catalyzed esterification with vinyl acetate. PS-Amano lipase was found to be highly efficient and gave the desired (*S*)-acetate in >99% ee. However, addition of allenylzinc bromide to the silyl-protected α-hydroxy aldehyde occurred in a non-selective manner, leading to a *syn*-*anti* mixture of the enyne target compound in a 4:7 ratio. The latter derivative was also a key intermediate for the synthesis of the allylic alcohol A-ring precursor, the exocyclic diene of which with (*Z*)-geometry was formed upon an intramolecular Heck reaction of the (*Z*)-vinyl iodide (Scheme 234).[301]



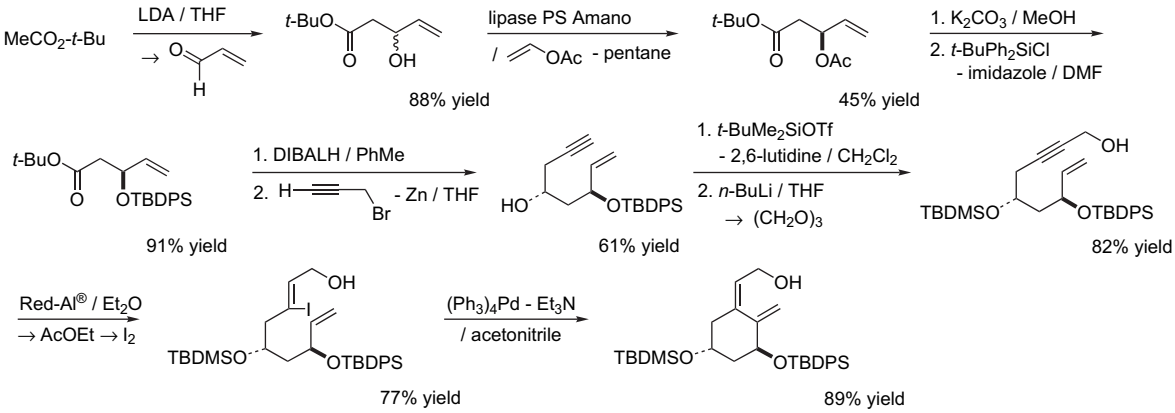
Scheme 231.



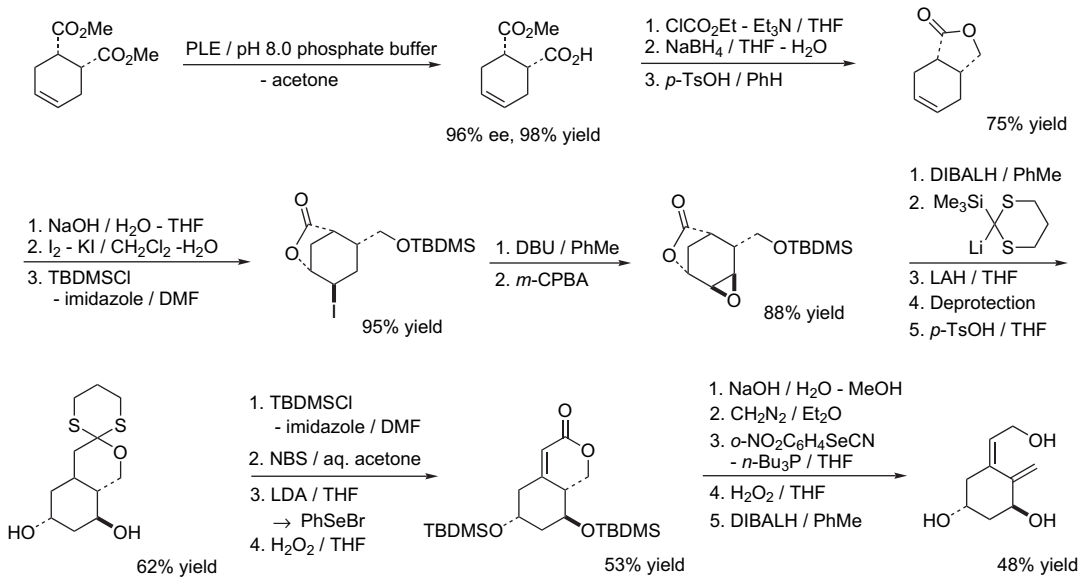
Scheme 232.



Scheme 233.



Scheme 234.

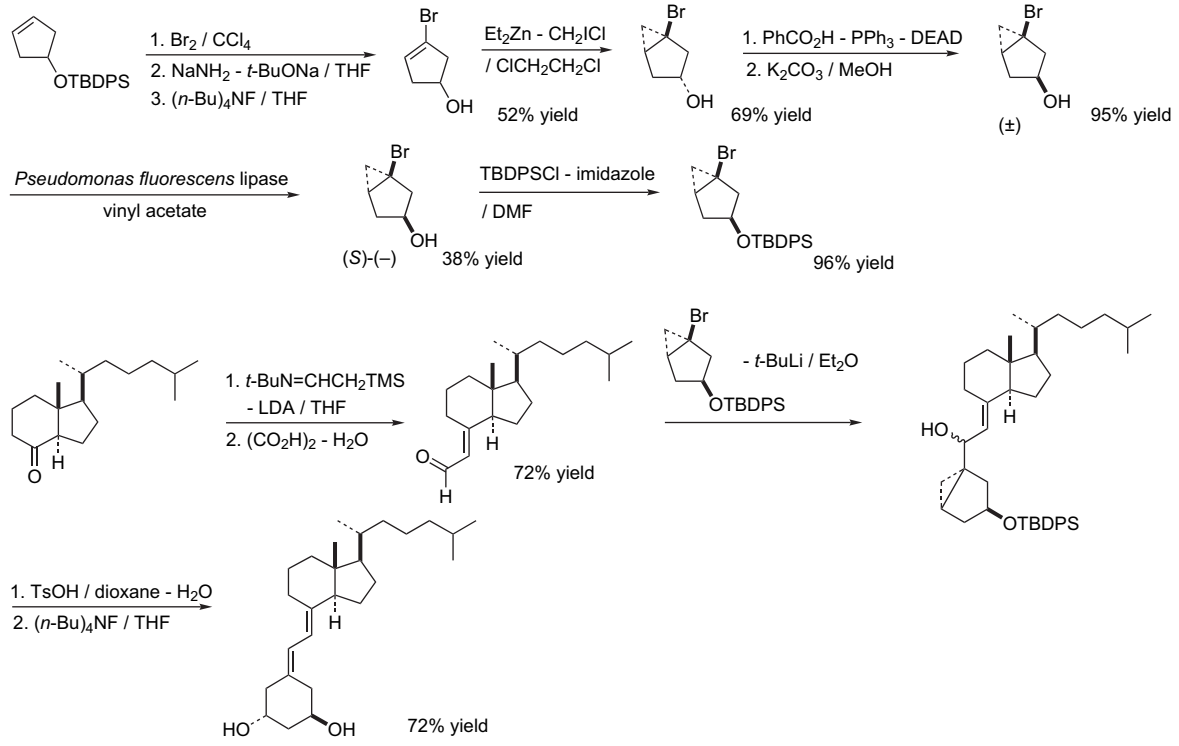


Scheme 235.

The resulting dienol could also be synthesized starting from a chiral monoester enzymatically generated by selective hydrolysis of the symmetric unsaturated *cis* diester with pig liver esterase (PLE). Hydroxyl groups at C(3) and C(1) were introduced by iodolactonization and selective epoxidation–reduction of the corresponding eliminated product (Scheme 235).[302]

Wu-Yong and Vandewalle prepared the optically active, 1-bromobicyclo[3.1.0]hexan-3-ol, by enzymatic kinetic resolution with *Pseudomonas fluorescens* lipase and vinyl acetate as an A-ring precursor for 19-nor-1α,25-dihydroxyvitamin D_3 analogs. In order to generate the diene unit, addition of the lithiated bicyclo[3.1.0]hexane, generated by lithium–bromide exchange, to the α,β-unsaturated aldehyde of Windaus–Grundmann ketone followed by acid-catalyzed sigmatropic rearrangement of the cyclovitamin gave rise to the vitamin D diene system in 72% yield (Scheme 236).[303]

Racemic 2-trimethylethynyl-2-cyclopentenol, an intermediate in the synthesis of 1α,25-dihydroxyvitamin D_3 required in the Wilson and Uskokovic approach, was resolved via



Scheme 236.

kinetic acetylation with vinyl acetate in the presence of lipase PS (Amano, *Pseudomonas* sp.) (Scheme 237).[304] Similarly, lipase-mediated resolution of racemic 2-carbethoxy-2-cyclopentenol furnished the optically pure (*R*)-acetate and (*S*)-alcohol and the requisite acetylene side chain was introduced employing the Fuchs–Corey method (Scheme 238).[305]

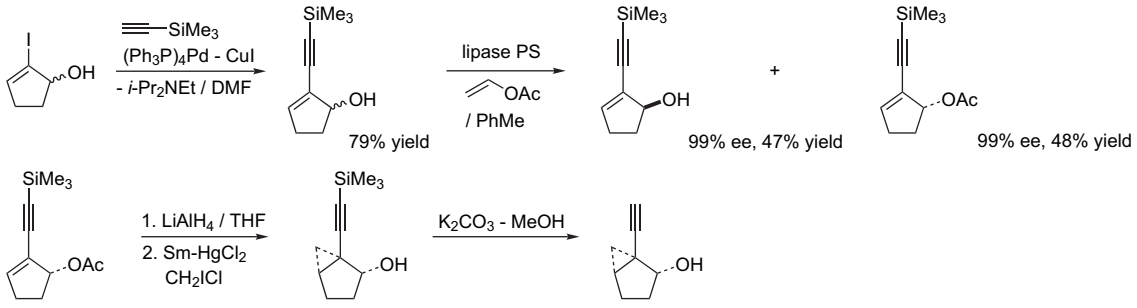
Kinetic resolution of 5-hydroxymethyl-3-methoxymethoxy-2-cyclohexenone using lipase-catalyzed enantioselective esterification of its primary alcohol group was reported by Yamada and co-workers to generate the chiral CD-ring *trans*-hydrindanone of 12-oxygenated steroid types of antitumor marine aragusterols. The formation of the expected bicyclic aliphatic intermediate was obtained by stereocontrolled inter- and intramolecular Michael addition reaction with a functionalized α,β-unsaturated ester, intramolecular pinacol coupling, and subsequent carbon–carbon bond cleavage through retro-aldol reaction (Scheme 239).[306]

As reported by Takano, the optically active (−)-tricyclic dienone, accessible from racemic dicyclopentadiene via allylic oxidation and lipase-mediated kinetic hydrolysis of the corresponding acetate,[307] was revealed to be an excellent dienophile to react regio- and diastereoselectively with Dane's diene in the presence of diethylaluminum chloride. Methylation of the *exo*-adduct at C(13) occurred exclusively from the convex face of the enolate, leading to the trans-fused CD-ring junction of natural steroid skeletons. Hydrogenation of the C(9)–C(11) double bond by triethylsilane and trifluoroacetic acid gave rise to the trans-BC fused product, which underwent a retro Diels–alder reaction upon heating. A few transformations liberated the (+)-estrone (Scheme 240).[308]

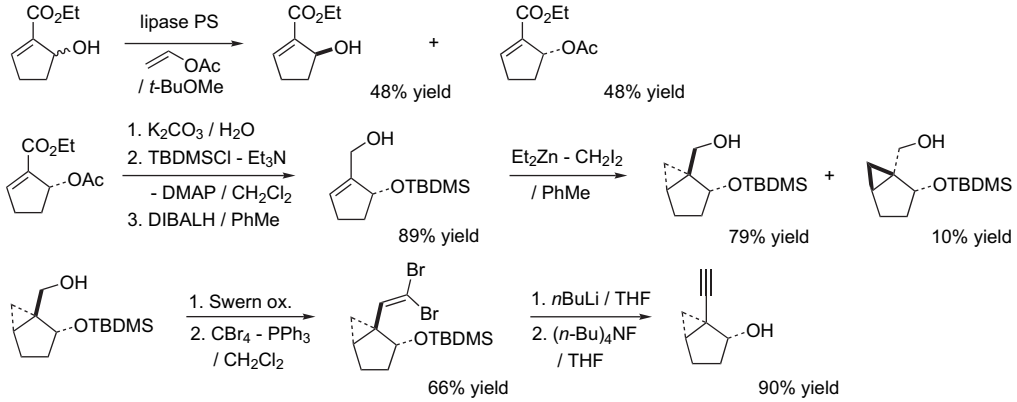
Two years earlier, Takano's research group had exploited the reactivity of the chiral cyclopentadienone synthon for the elaboration of the estrogenic steroid, (+)-equilenin. The reaction sequence started with the 1,4-addition of a naphthalene-derived Grignard reagent catalyzed by copper(I) iodide followed by metallo-enamine formation and two successive alkylations with allyl bromide and methyl iodide, respectively. Upon thermolysis, the seco-C steroid was liberated and converted into (+)-equilenin via a Pummerer-type cyclization as a key step (Scheme 241).[309]

Steroid-derived natural products such as nicandrenones have been synthesized by Corey and co-workers. The Amano lipase PS-mediated kinetic resolution of the racemic *cis*-3-silylated cyclohexanol was used to prepare the corresponding enantiomerically pure α,β enone, which was engaged in an unusual *exo* selective Diels–Alder process. A series of functional-group manipulations transformed the tetracyclic nicandrenone nucleus and the elaboration of the complex side chain involved a key CBS reduction of an ynone (Scheme 242).[310]

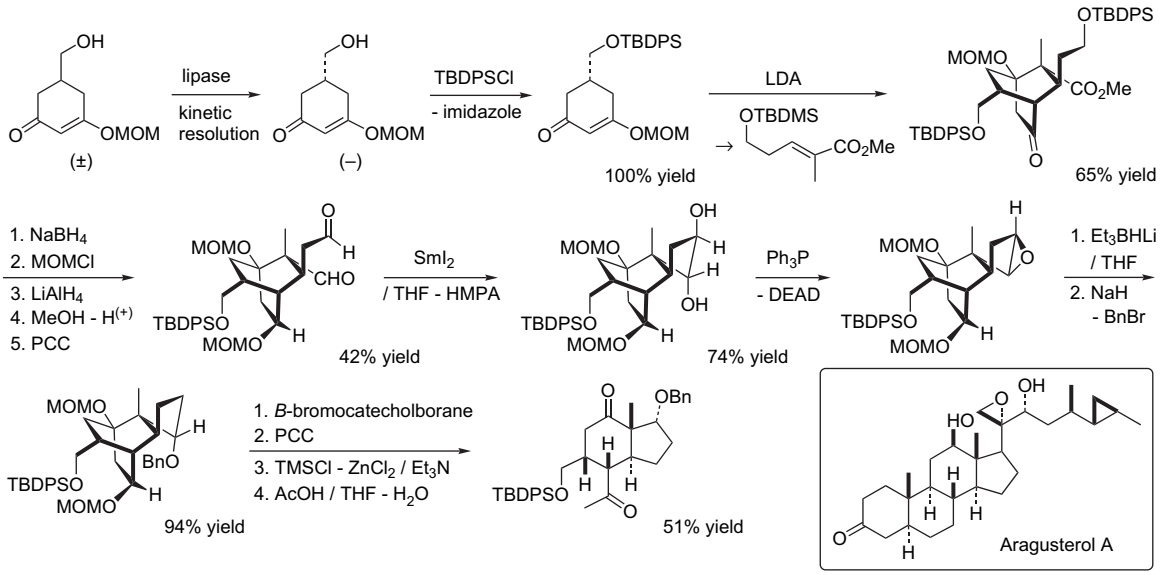
In 1978, Rosenberger and co-workers achieved the construction of the optically pure (−)-17β-hydroxy-des-A-androst-9-en-5-one, a BCD-tricyclic steroid precursor, starting from a chiral δ-lactone readily obtained by selective microbiological reduction of the prochiral 5-keto heptanoic acid with a culture of *Margarinomyces bubaki*. On sequential vinylmagnesium chloride addition, diethylamine trapping,



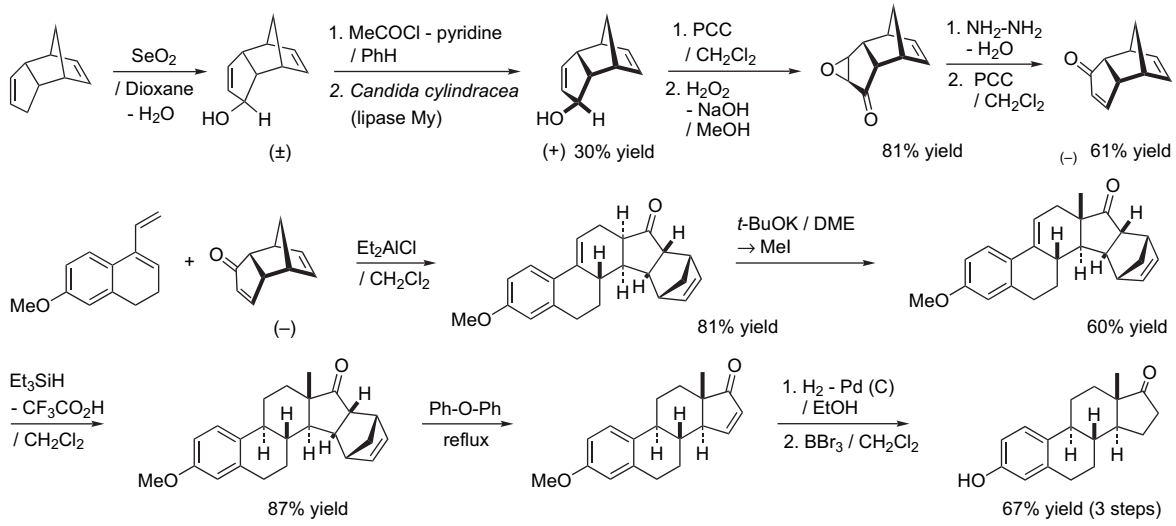
Scheme 237.



Scheme 238.



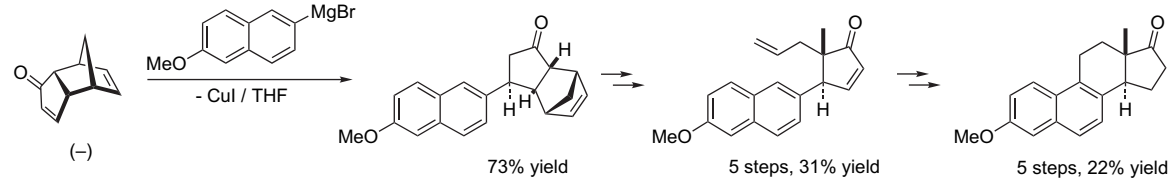
Scheme 239.



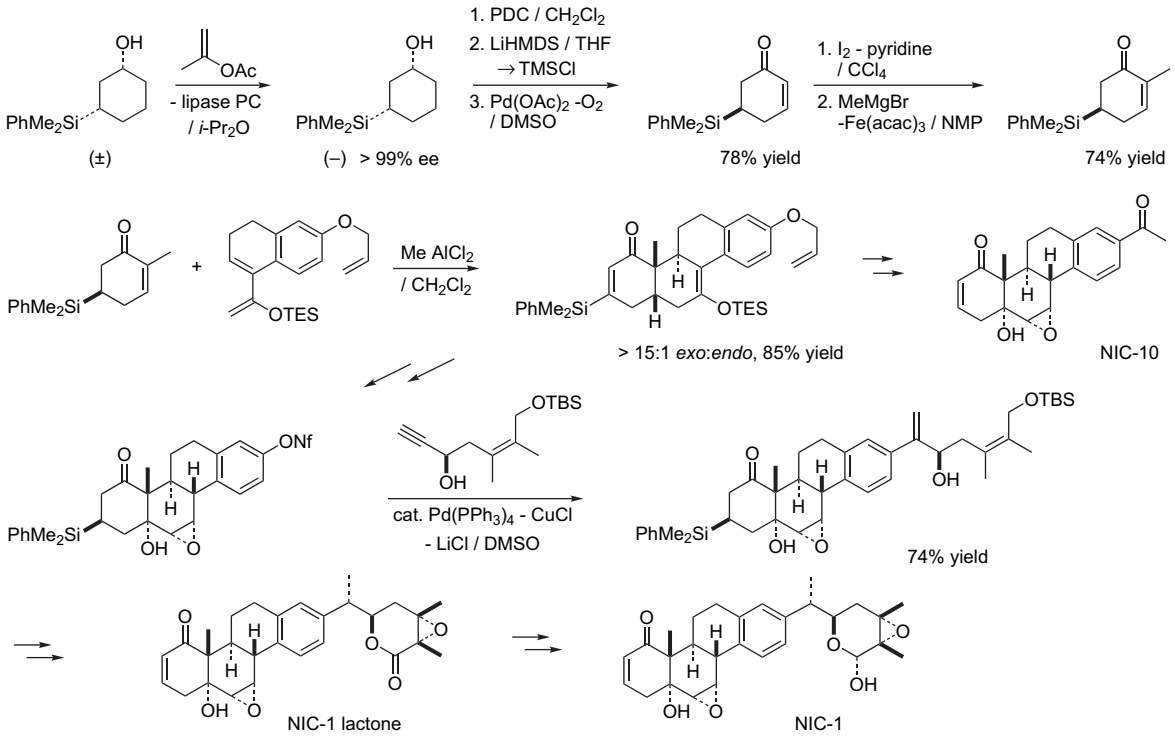
Scheme 240.

and mild acid treatment, the crude oxime ether afforded a masked Mannich base, which was condensed with 2-methyl-cyclopentane-1,3-dione to give predominantly the 13β-*trans* diene. Suitable manipulations of this key substrate, depicted in Scheme 243, led to the target tricyclic adduct.[311]

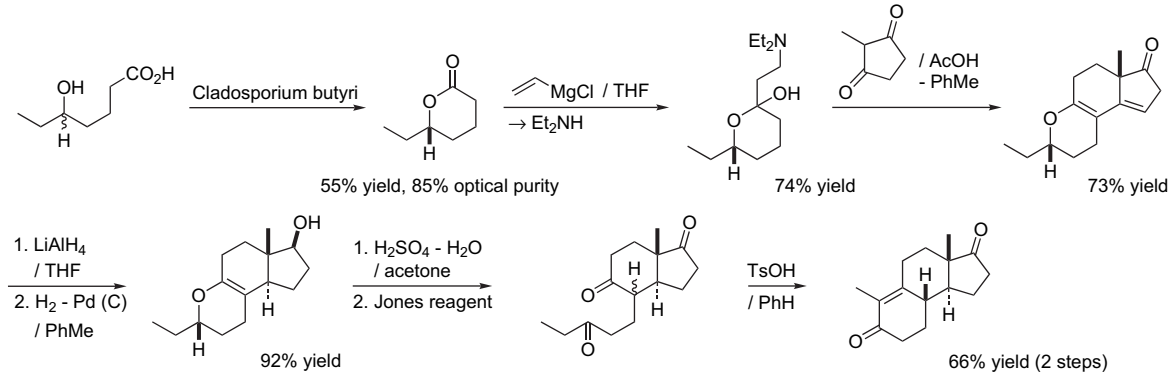
A variety of 7-methyl-19-nor-steroids were synthesized by Cai and co-workers through alkylation of a CD-ring fragment indenone with a chiral tosylate derived from the product of asymmetric reduction of 1-(3-methoxy-phenyl)-2-propanone by *Saccharomyces cerevisiae*. Subsequent hydrogenation gave the *trans*-perhydroindane, which cyclized to produce the complete tetracyclic steroid skeleton. The natural trans-*anti*-trans arrangement was established after a second hydrogenation and led to the 7α,18-dimethyl estradiol derivative (Scheme 244).[312]



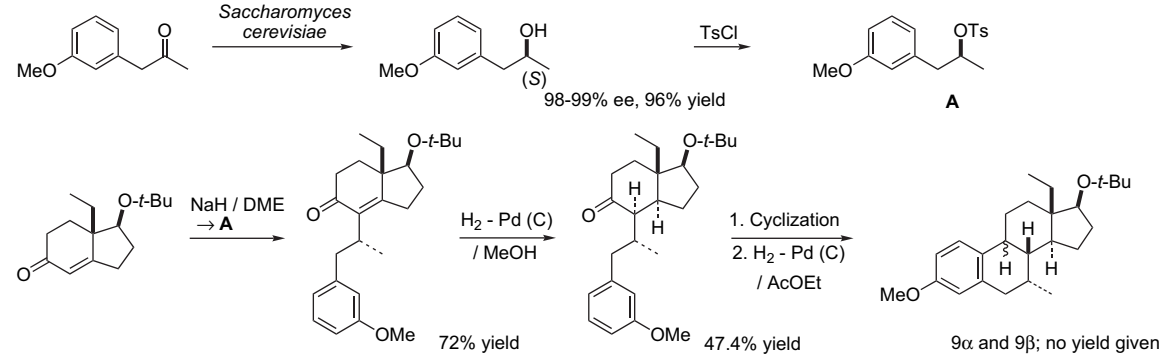
Scheme 241.



Scheme 242.



Scheme 243.



Scheme 244.

Acknowledgements

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Biographical sketch

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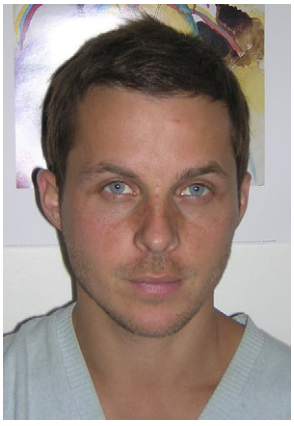

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Cyril Ollivier was born in Neuilly (France) in 1971. He received his Diplôme d'Etudes Approfondies in Organic Chemistry from Pierre and Marie Curie University (Paris VI) under the guidance of Prof. J.-F. Normant and Dr. F. Chemla in 1995, working on the reactivity of carbenoids in 1,2-metalate rearrangement. After one year of national service at the ENSTA (Paris) as scientist associate in the laboratory of Dr. L. El Kaim, he joined Prof. Ph. Renaud's group at the University of Fribourg (Switzerland) in 1996 for a Ph.D. program in collaboration with the laboratory of Prof. M. Malacria (Paris VI). He worked on the utilization of organoboranes as source of radicals, on the developments of novel radical hydroxylation and azidation processes, and gained his doctorate in cotutelle in 2000. He was awarded a Swiss National Foundation Fellowship to pursue research studies at the University of Texas at Austin (Austin, TX) in Prof. Ph. Magnus' group where he was involved in the total synthesis of guanacastepene. In 2002, he joined the CNRS at Aix-Marseille University where he worked with Prof. M. Santelli. His research focused on the reactivity of allylsilanes and the synthesis of steroids, particularly vitamin D analogs. Since January 2007, he is developing new directions for research on radical and organometallic chemistry, in Prof. M. Malacria's group (Paris VI).

Maurice Santelli was born in Marseille. He is graduated in chemistry from Ecole Supérieure de Chimie de Marseille (1961) become recently Ecole Centrale Marseille. He received his Ph.D. in chemistry working with Prof. M. Bertrand (homoallenylic participation, non-classical ions). He had a postdoctoral position at the University of Cambridge (U.K.) in 1973 (Prof. R. A. Raphael). After an appointment at the University of Oran (Algeria) (1975–77), he is presently Prof. of Chemistry at the Aix-Marseille University. His main research areas are physical organic chemistry, electrophilic activation, allylsilane chemistry (Bistro…), palladium-chemistry with new ligands (Tedicyp…), and the synthesis of bioactive products (polyunsaturated fatty acids, Prelog-Djerassi lactone, non-natural steroids…).