Tetrahedron 65 (2009) 7001–7015

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stereoselective synthesis of CD-ring precursors of vitamin D derivatives

Raphaël Rodriguez, Anne-Sophie Chapelon, Cyril Ollivier *,†, Maurice Santelli *

Laboratoire de Synthèse Organique (Equipe Chirosciences, associée au CNRS), Université d'Aix-Marseille, Faculté des Sciences de St-Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

ARTICLE INFO

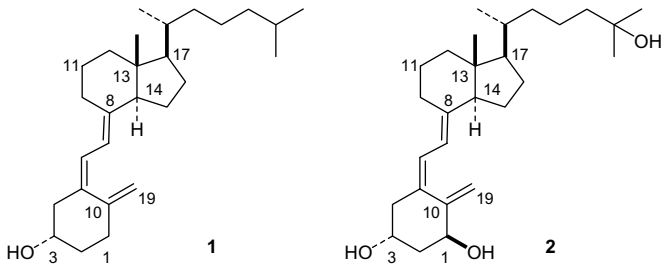
Article history:
Received 6 April 2009
Received in revised form 7 June 2009
Accepted 12 June 2009
Available online 18 June 2009

ABSTRACT

Two expedious and useful approaches to the construction of Vitamin D *trans*-hydrindane building blocks are proposed. These involve the desymmetrization of the *anti meso*-acetylmethyldivinylcyclopentane **3** which proceeds through either the selective formation of epoxyketone **5** and intramolecular enolate cyclisation or a xanthate groupe transfer mediated radical cyclization to furnish *trans*-hydrindanes **7** and **16** respectively. Epoxyketone **5** is prepared by means of a three-step reaction process including reduction of the ketone moiety, bishomoallylic alcohol-directed epoxidation and Dess–Martin oxidation. Alternatively, an asymmetric reduction using borane/tetrahydrofuran complex and (*R*)-2-methyl-CBS-oxazaborolidin made accessible the epoxyketone in good optical purity. The xanthate **16** can undergo a Johnson sulfoximine ketone resolution that allows access to both enantiomers. Various derivatizations of **16** to more elaborated synthetic intermediates are also reported.

1. Introduction

Vitamin D_3 **1** and its metabolites, more particularly the natural hormone 1α,25-dihydroxyvitamin D_3 or calcitriol **2** (Scheme 1), have attracted considerable attention because of their remarkable biological activity in such areas as regulation of calcium and phosphorus metabolism, cellular differentiation, inhibition of cell proliferation implied in cancers or other hyperproliferation diseases, and immunology.[1] However, the use of 1α,25-dihydroxyvitamin D_3 as antitumor agent was hampered by toxic hypercalcemia side effects. Therefore, analogs that do not disrupt the phosphocalcic homeostasis are required.[2] For this reason, preparation of highly-potent vitamin D_3 analogs has attracted the interest of numerous synthetic groups.[3] More recently, new compounds showed promise in the treatment of a variety of diseases as diverse as psoriasis, renal osteodystrophy, osteoporosis, diabetes, leukemia, cancer (breast, colon, prostate), AIDS and multiple sclerosis.[4]



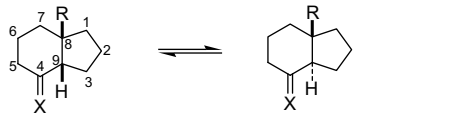
Scheme 1. Representation of vitamin D_3 **1** and calcitriol **2**.

Early generation vitamin D analogs have traditionally been prepared from steroid precursors or vitamin D_2. A versatile method pioneered by Lythgoe has been used intensively for the preparation of vitamin D_3 and highly functionalized analogs. This pioneer work initiated a range of efficient strategies for the preparation of 1α,25-dihydroxyvitamin D_3 derivatives modified at specific positions involving cross-coupling between A rings and CD bicyclic hydrindanes.[3]

Despite the large number of synthetic methods known for constructing these *trans*-hydrindane CD-ring building blocks,[5] innovative, efficient and straightforward approaches to polyfunctionalized units, with a C_{13}–C_{14} trans-junction and a cis relationship between the substituents at C_{13} and C_{17} carbon centers,[6] still represents a synthetic challenge.[7] In fact, steroidal *trans*-8-methyl-4-hydrindanones, such as the Grundman–Windaus ketone obtained from ozonolysis of vitamine D_3, turned out to be less stable than the cis form by approximatively 0.76–1.45 to 2.36 kcal/mol depending on the literature source (Scheme 2),[8–10] then the trans-ring junction can be easily epimerized under acidic or basic conditions.[11]

* Corresponding authors. Tel.: +33 491288825; fax: +33 491289112 (M.S.); tel.: +33 144272547; fax: +33 144277360 (C.O.).
E-mail addresses: cyril.ollivier@upmc.fr (C. Ollivier), m.santelli@univ-cezanne.fr (M. Santelli).
† Present address: UPMC Univ Paris 06, UMR CNRS 7201, Institut Parisien de Chimie Moléculaire, 4 place Jussieu, C. 229, F-75005 Paris, France.

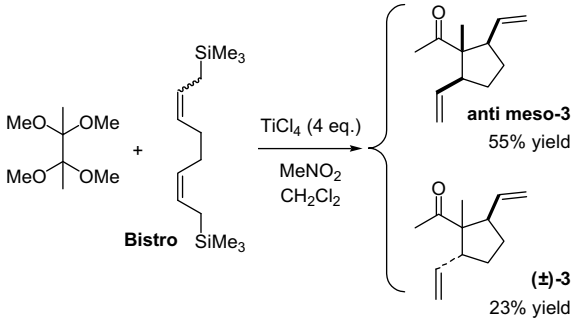
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.06.052



Scheme 2. Stability *cis*- versus *trans*-hydrindane.

2. Access to polyfunctionalized *trans*-hydrindane units from stereoselective epoxidation of the *anti meso*-acetylmethyldivinylcyclopentane

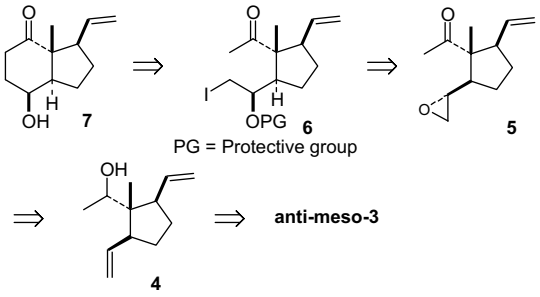
Some years ago, we described the synthesis in 78% yield (47% yield on 0.8 mol scale) of acetylcyclopentanes *anti-meso*-**3** and (±)-**3** from easily available 1,8-bis(trimethylsilyl)-2,6-octadiene (Bistro)[12] and 2,2,3,3-tetramethoxybutane in the presence of $TiCl_4$ (Scheme 3). To explain its formation, we suggested that a titanium tetrachloride-mediated S_E2' substitution followed by a pinacol-type rearrangement of the divinyl intermediate should operate.[13]



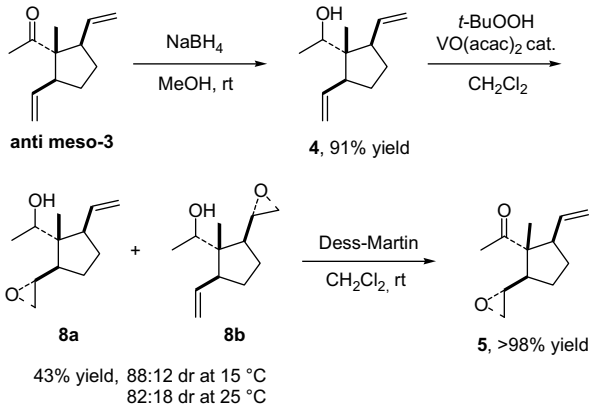
Scheme 3. Preparation of divinylacetylcyclopropanes *anti meso*-**3** and (±)-**3** from 2,2,3,3-tetramethoxybutane and Bistro.

In connection with our interest in steroids synthesis, and particularly in vitamin D synthesis,[14] we decided to explore new strategies for the stereoselective preparation of highly functionalized *trans*-hydrindane units starting from the versatile building block *anti-meso*-acetylmethyldivinylcyclopentane *anti-meso*-**3**.[14b,c] We first tried to build the 6-membered ring of the CD bicyclic moiety in a trans fashion by cyclization of the protected iodohydrin **6** through intramolecular enolate alkylation. This intermediate could be constructed from the corresponding epoxyketone **5**, which could be obtained by stereoselective desymmetrization of *anti-meso*-**3**. The latter could be realized through a three step sequence involving sequential ketone reduction, bishomoallylic alcohol-oriented monoepoxidation[15] and reoxidation of alcohol providing the epoxyketone **5** as a single diastereoisomer. Interestingly, **7** should present a structure and relative stereochemistry similar to the Inhoffen–Lythgoe diol functionalized at the C_{12} position (Scheme 4). It was demonstrated that the 12-oxygenated functionality or 12-methyl plays an important role in the antitumor activity.[16]

Our first task was the diastereoselective synthesis of epoxyketone **5** from *anti-meso*-**3** as shown in Scheme 5. Methyl ketone reduction of *anti-meso*-**3** with $NaBH_4$/MeOH was followed by a bishomoallylic alcohol-oriented epoxidation of **4** with $VO(acac)_2$/*t*-BuOOH to furnish an inseparable mixture of epoxides **8a** and **8b** in 43% yield (63% based upon recovered **4**) with a 88:12 dr for reactions run at 15 °C and a 82:18 dr at 25 °C.[17] These diastereomeric ratios, measured by means of GC, showed to be slightly dependent



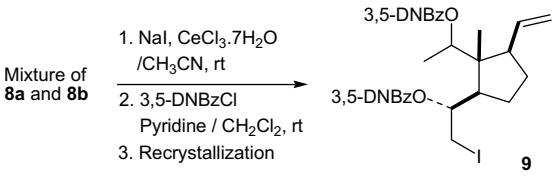
Scheme 4. Retrosynthetic approach for the preparation of the *trans*-hydrindane unit **7** from the *anti meso*-**3**.



Scheme 5. Diastereoselective synthesis of epoxyketone (±)-**5** from *anti meso*-**3**.

on the reaction temperature. Subsequent Dess–Martin oxidation[18] of the mixture of **8** gave the targeted epoxyketone **5** as a single diastereoisomer.

The relative configuration of the major epoxyalcohol **8a** was elucidated by X-ray diffraction analysis of a derivative. In fact, the mixture of epoxides **8a** and **8b** was converted into the corresponding crystalline bis-(3,5-dinitrobenzoyloxy)iodohydrin derivative **9**. After recrystallization of the mixture, the major isomer **8a** was isolated and gave pure cristals suitable for X-ray cristallography. Figure 1 shows an ORTEP representation of **9**.



From *anti-meso*-**3**, the initial methyl ketone reduction in secondary alcohol generates a new stereogenic center which induces discrimination between both vinyl groups in the bishomoallylic alcohol-oriented epoxidation process, as illustrated in Scheme 6. As we observed, the bishomoallylic alcohol/$VO(acac)_2$/TBHP chelate complexe C_1 was preferentially formed. The total discrimination between both faces of each vinyl group in favor of the A face can be explained by the fact that the rotation of the vinyl group is limited by the steric hindrance of the angular methyl and renders its B face inaccessible.

Scheme 7 depicts the final stages of the elaboration of the C ring. The above epoxyketone intermediate **5** was converted to iodohydrin **10** in 91% yield via a cerium trichloride-assisted regioselective ring opening of the epoxide by NaI.[19] Subsequently, protection of

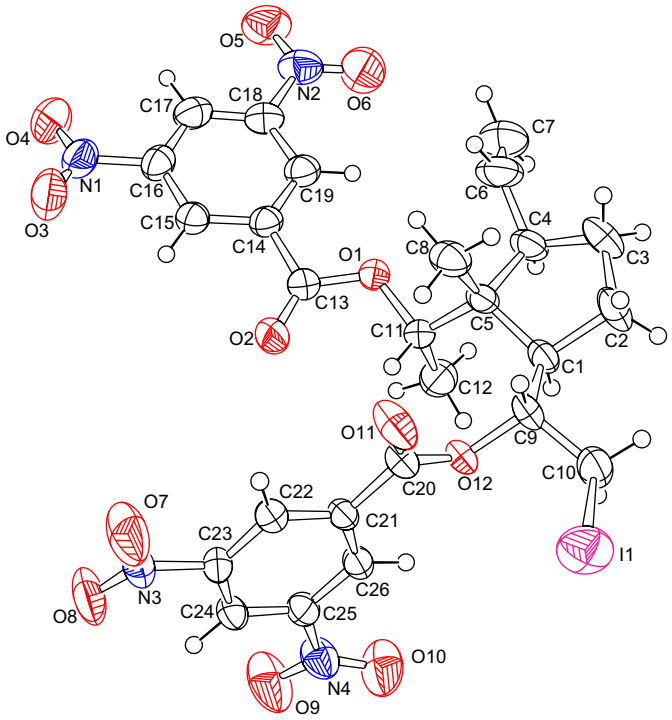
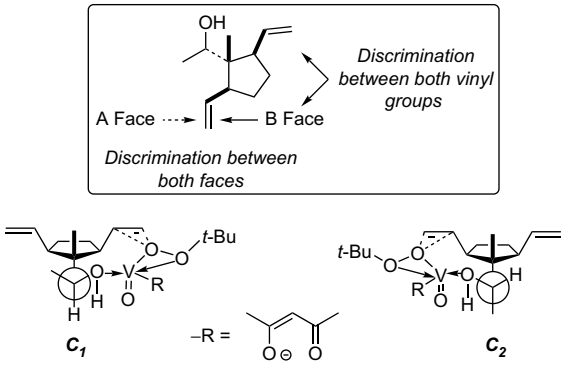
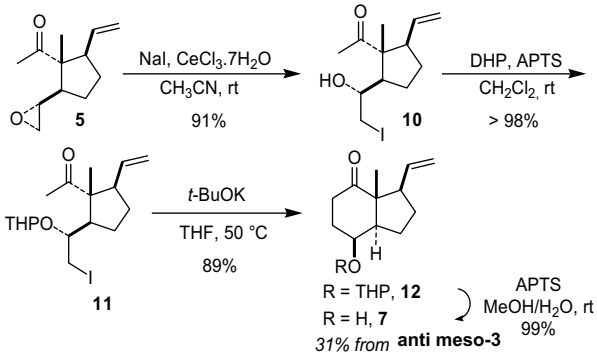


Figure 1. ORTEP drawing of X-ray structure of **9** with labeled heteroatom. Thermal ellipsoid are scaled to 50% probability level. Hydrogen atoms are drawn to an arbitrary scale.



Scheme 6. Two diastereomeric transition states for the $VO(acac)_2$/TBHP-catalyzed bishomoallylic alcohol epoxidation.



Scheme 7. Synthesis of a *trans*-hydrindane unit from **7**.

the hydroxyl group as a THP ether was carried out. To construct the 6-membered ring of the hydrindane, intramolecular ketone enolate alkylation of the δ-iodoketone adduct **10** was then performed. Potassium enolate, generated by treatment of **11** with *t*-BuOK/THF at 50 °C, underwent a rapid 6-*exo*-*tet* cyclization involving nucleophilic substitution of iodide and gave rise to the hydrindane **12** in 89% yield.[20] Removal of the THP protective group liberated the polyfunctionalized hydrindane bicyclic compound **7** (Scheme 7, Fig. 2).

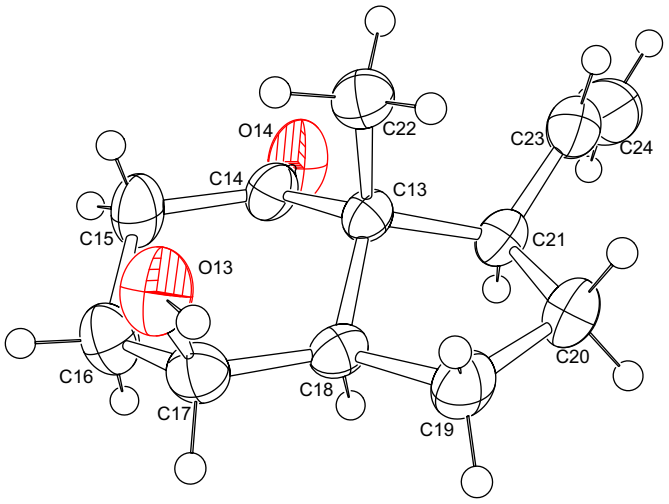
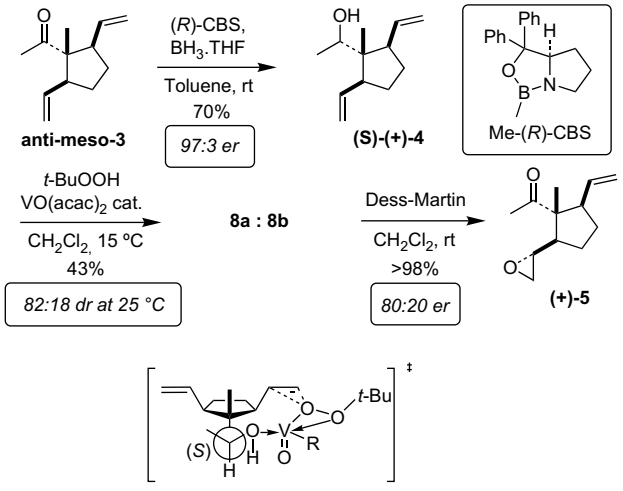


Figure 2. ORTEP drawing of X-ray structure of **7** with labeled heteroatom.

A formal enantioselective access to this hydrindane, showing the absolute configuration of the natural vitamin D_3 at C_{13}, C_{14} and C_{17}, is proposed with the asymmetric synthesis of the epoxyketone (+)-**5** (Scheme 8). An approach based on catalytic CBS-reduction[21] followed by a similar bishomoallylic alcohol-oriented epoxidation—Dess–Martin oxidation sequence has been investigated. The enantioselective reduction of the methyl ketone moiety with borane/tetrahydrofuran (BH_3·THF) and a chiral oxazaborolidine (Me-(*R*)-CBS) as catalyst at rt furnished the secondary alcohol (*S*)-(+)-**4** in a good 70% yield and high optical purity (>99:1 to 97:3 er, determined by chiral GC). According to the intensive studies of Corey and co-workers[21] on catalytic CBS reduction of methyl ketones, the (*S*) absolute configuration of (+)-**4** can be assigned on the basis of the known facial selectivity of the reducing agent. Regardless to the nature of the ketone, the level of asymmetric induction is in accordance with the earlier examples reported in the litterature. We then applied the previous $VO(acac)_2$-mediated TBHP epoxidation procedure to the enantiomerically enriched alcohol

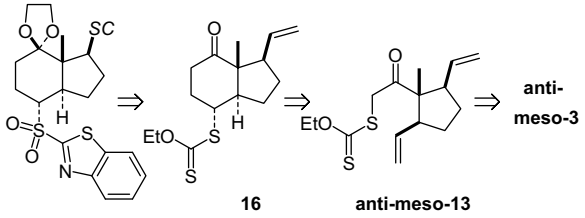


Scheme 8. Asymmetric approach to epoxyketone (+)-**5**.

(+)-**4**, leading to a 82:18 mixture of epoxyalcohols **8a** and **8b** at 25 °C.[22] During the process, a chiral transfer involving the reported transition state was operating as the er was conserved. This result was proved by chiral GC analysis. Finally, oxidation using Dess–Martin reagent liberated the corresponding product (+)-**5** in 80:20 er.[23]

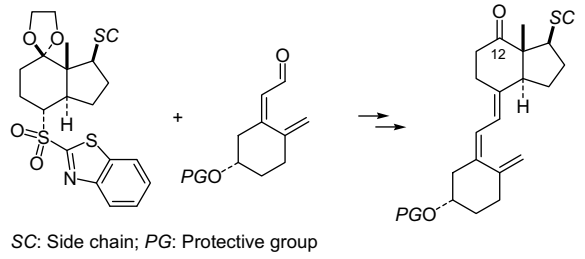
3. Access to *trans*-hydrindane units from the *anti meso*-acetylmethyldivinylcyclopentane involving a radical pathway

According to the retrosynthesis shown in Scheme 9, elaborated vitamin D *trans*-hydrindane building blocks can also be obtained in a straightforward way from the radical cyclization of dithiocarbonate *anti-meso*-**13** and starting from *anti-meso*-**3**.[14c]



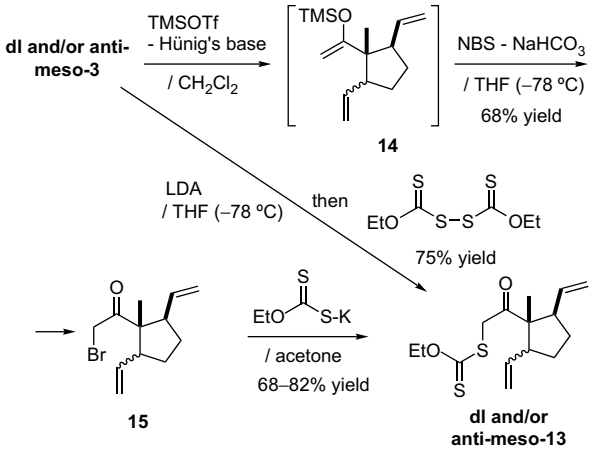
Scheme 9. Retrosynthetic analysis for the synthesis of *trans*-hydrindanes as precursors of vitamin D analogs.

Then, the coupling between these building blocks and a suitable aldehyde according to the Kocienski-modified[24,25] Julia olefination reaction[26] should allow the construction of the trienic system vitamin D and its analogs (Scheme 10) as already reported in the literature.



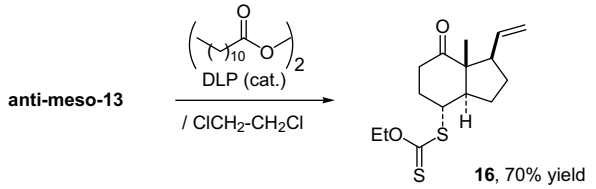
Scheme 10. Construction of the trienic part of vitamin D analogs by using a Julia-Kocienski olefination coupling.

The main step of our strategy consists of a dithiocarbonyl group transfer cyclization, based on the degenerative radical exchange of a xanthate group, extensively developed by Zard and coworkers.[27,28] We intend to examine the applicability of this methodology on xanthate *anti-meso*-**13** featuring its desymmetrization through a selectively functionalization of one vinyl group. The suitable acetyl xanthate derivative *anti-meso*-**13** can be obtained by either nucleophilic substitution of the bromine atom of the α-bromoketone *anti-meso*-**15** with the commercially available potassium *O*-ethyl xanthogenic salt or directly by reaction of diethyl bisdithiocarbonate $(SC(S)OEt)_2$ with lithium ketone enolate of *anti-meso*-**13**. As the separation of *anti-meso*-**13** and (±)-**3** by flash column chromatography or by distillation is difficult on multigram scale,[29] experiments have been led from the mixture with then separation of products or on small quantities of pure acetylcyclopentane *anti-meso*-**3**. Treatment of a mixture of *anti-meso*-**3** and (±)-**3** or the sole *anti-meso*-**3** with TMSOTf/Hünig's base/CH_2Cl_2 followed by reaction with NBS/$NaHCO_3$/THF at −78 °C gave the bromides **15** (68–76%) which were placed in the presence of an excess of KSC(S)OEt in acetone affording the xanthates **13** (68–82%).[28a] However, the latter can be readily prepared in 75% yield by quenching the lithium enolate of **3** with $(SC(S)OEt)_2$ (Scheme 11).[30]

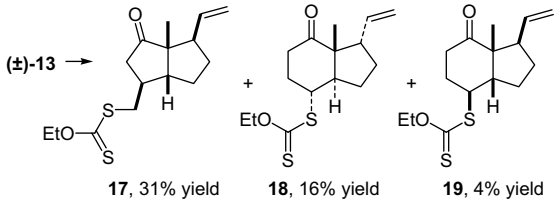


Scheme 11. Preparation of dithiocarbonate *anti-meso*-**13** and (±)-**13**.

When xanthate *anti-meso*-**13** was heated in degassed 1,2-dichloroethane in the presence of lauroyl peroxide (DLP) (20 mol% added portion wise), an intramolecular cyclization occurred leading to the expected hydrindanone **16** in good yield and with total stereoselectivity (Scheme 12). From the xanthate (±)-**13**, the cyclization reaction led to a more complex mixture in which the major compound was diquinane **17**, besides the *trans*-hydrindanone **18** and the *cis*-hydrindanone **19** (Scheme 13). Moreover, yields were moderate (overall yield, 51%) and the reaction required a large amount of lauroyl peroxide (50 mol%) for completion of the reaction. Consequently, when the reaction was performed on multigram scale (20 mmol) with the mixture of *anti-meso*-**13** and (±)-**13** (70:30 *meso*/*dl*), **16** as well as **17** were easily isolated in 59% and 14% yields, respectively together with only traces of **18** and **19** (<5%).

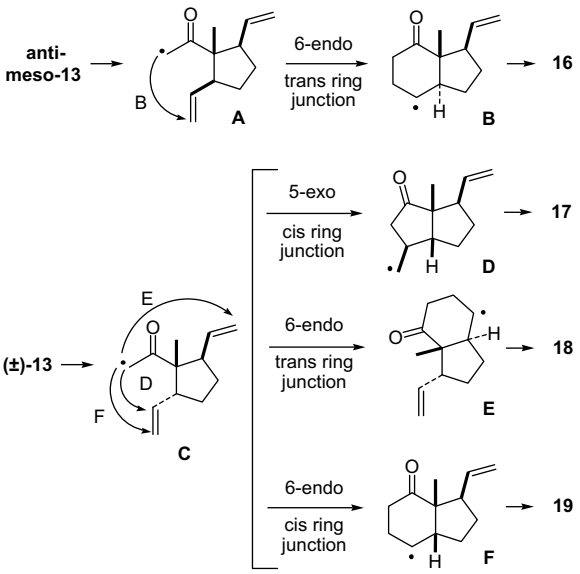


Scheme 12. Cyclization reaction of *anti-meso*-**13**.



Scheme 13. Cyclization reaction of (±)-**13**.

The formation of *trans*-hydrindanone **16** can be explained by the following mechanism outlined in Scheme 14 where the α-carbonyl radical **A**, obtained from *anti-meso*-**13** during the initiation step by action of a lauroyl radical, undergoes a selective 6-*endo*-*trig* cyclization with one of both vinyl groups. Usually, 5-hexenyl radicals cyclize with high regioselectivity to give five-membered ring rather than six-membered ring.[31] However, acyclic 2-oxo-5-hexenyl radicals have been shown to evolve through a preferential 6-*endo*-*trig* cyclization pathway via a chair-like transition state leading to the corresponding cyclohexanones.[32,33] Indeed, as reported in the literature, MM2 Calculations investigated by Houk match the experimental results and confirm this unexpected regioselectivity of the



Scheme 14. Radical intermediates involved in cyclizations of *anti-meso*-**13** and (±)-**13**.

radical cyclization.[34] Thus, the transient secondary radical **B** can propagate the radical chain by xanthate group transfer. The stereoselectivity of the xanthate moiety at the C-4 position, confirmed by ^{1}H NMR and NOESY experiments, is modulated by the 1,3-diaxial interaction with the angular methyl at C-8 favoring an equatorial attack of the radical **B** onto the xanthate group of another molecule of **13** during the chain process.

Contrary to *anti-meso*-**13**, the α-carbonyl radical **C**, generated from (±)-**13**, evolved through three different cyclization pathways depending on the cyclization mode and the vinyl implicated. A significant quantity of *cis*-fused bicyclic cyclization product **17**, resulting from a 5-*exo*-*trig* cyclisation process, and the 6-*endo*-*trig* compound **19** were formed in an 8:1 ratio. The diquinane **17** was obtained as a unique diastereomer whose relative stereochemistry was corroborated by NOESY experiments. Presence of the adduct **18**, resulting from a 6-*endo*-*trig* closure with the other vinyl substituent in a trans relationship with the acetyl group and leading to a trans-fused compound, was also detected without any trace of the corresponding 5-*exo*-*trig* cyclization product. This inversion of selectivity giving a 5-*exo*/6-*endo* ratio of 8:5 in favour of the five-membered ring formation was rationalized by calculations as follows.

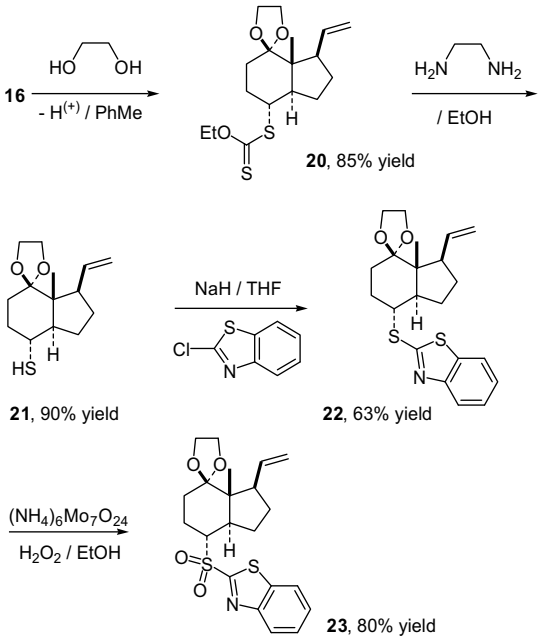
We have determined the relative enthalpies of reactant radicals A (from *anti-meso*-**13**) and C (from (±)-**13**) and radicals resulting from the cyclization using DFT calculations at the UB3LYP/6-311G++(d,p) level of theory.[35] Density functional theory calculations have been performed using Gaussian 03, revision D.02.[36] From calculations, we note that the radical **A** is weakly more stable that its isomer **C** (ΔE ~1 kcal/mol). All the cycloadditions are weakly exothermic. Curiously, the diquinane derivative primary radical **D** is particularly stable. In fact, radical **C** mainly reacted with the *cis*-vinyl group and the more proximal carbon atom (**D**/**F**=7.75:1) (near-attack conformation[37] or 'propinquity' effect[38]). The topochemically controlled structure of **C** is in accordance with the Bürgi–Dunitz trajector[39] and in this way minimizes both the entropic and enthapic contributions of the free energy of the transition state leading to **D**. At the UB3LYP/6-311g(d,p) level, for the more stable conformation of the radical **C**, the distance between the acyl radical carbon atom and the methine carbon atom of the *cis*-vinyl group (attack **D**) is equal to 3.52 Å, and the value of the corresponding Bürgi–Dunitz angle is 112.2° (with *trans*-vinyl group, 4.40 Å and 102.7°, respectively) (Table 1).

Table 1
Reactions enthalpies for the cyclizations computed at the UB3LYP/6-311G level

Radical	Total energy (hartree)	Zero-point energy[a] (hartree)	ZPE corr. (hartree)	Total energy with ZPE corr. (hartree)	Energy difference (kcal/mol)
A	−542.785301	0.257681	0.254846	−542.530454	
B	−542.800363	0.259685	0.256828	−542.543535	**A**→**B**=−8.21
C	−542.783651	0.257542	0.254709	−542.528943	
D	−542.802081	0.258340	0.255500	−542.546583	**C**→**D**=−11.07
E	−542.799215	0.259714	0.256857	−542.542358	**C**→**E**=−8.42
F	−542.807466	0.260512	0.257646	−542.549820	**C**→**F**=−13.10

[a] (ZPEs) are scaled by a factor of 0.989, as recommended for calculation at the Becke3LYP/6.311G(3df,2p) level.[40]

After successful formation of the *trans*-hydrindane ring skeleton **16**, we explored its various functionalization. First, preparation of the advanced intermediate **23**, as a potent precursor for the Julia–Kocienski coupling reaction, was accomplished through derivatization of the xanthate moiety in a benzothiazole sulfonyl group (Scheme 15). The ketone was first protected as its ethylene ketal and subjected to ethylene diamine in ethanol to liberate **21** as a free thiol.[41] Deprotonation of the thiol with sodium hydride in THF and subsequent reaction with 2-chlorobenzothiazone generated the corresponding 2-thiobenzothiazole adduct **22**.[42] This latter was oxidized[24c] with $(NH_4)_6Mo_7O_{24}$ (cat.)/H_2O_2/EtOH to give the sulfonyl derivative **23** (80%) of which the structure has been secured by X-ray crystallographic analysis (Fig. 3).



Scheme 15. Preparation of an advanced intermediate for the Julia–Kocienski coupling.

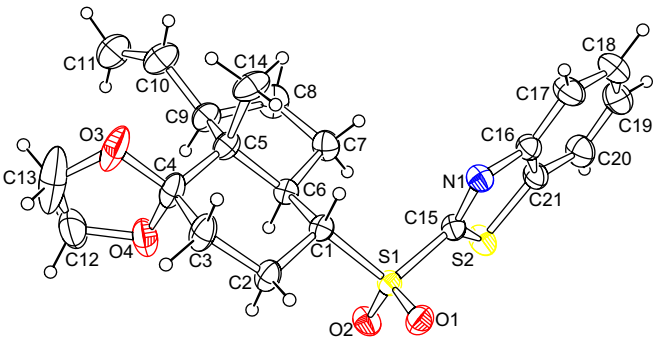
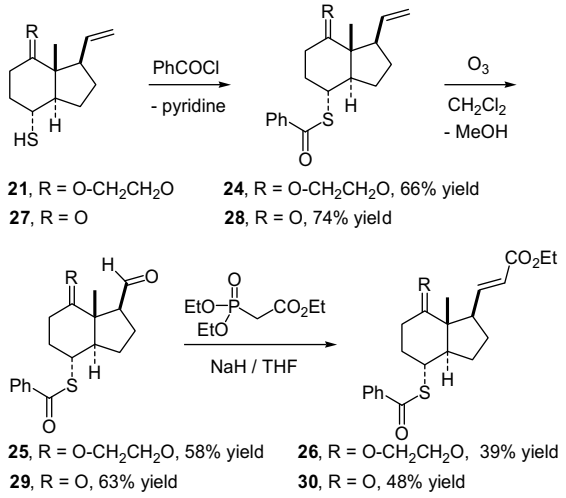


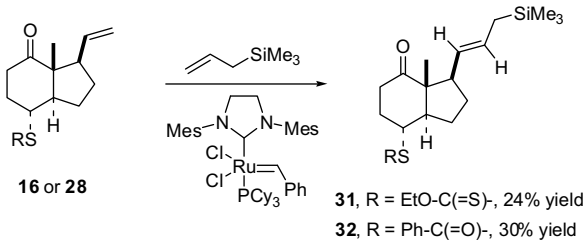
Figure 3. ORTEP drawing of X-ray structure of **23** with labeled heteroatoms.

Then, we used the 17-vinyl group of **24** or **28** for the side chain attachment according two different strategies. First, the thiol function of **21** or **27** was protected as thiobenzoyl esters **24** or **28**.[43] Ozonolysis[44] of these latter gave aldehydes **25** or **29** which were suitable substrate for a selective Wittig–Horner–Emmons reaction.[45] Only one diastereomer **26** or **30** was formed, confirming that no epimerisation occurred at the 17-position (Scheme 16).



Scheme 16. Functionnalization of the vinyl group by a ozonolysis/Wittig–Horner–Emmons olefination sequence.

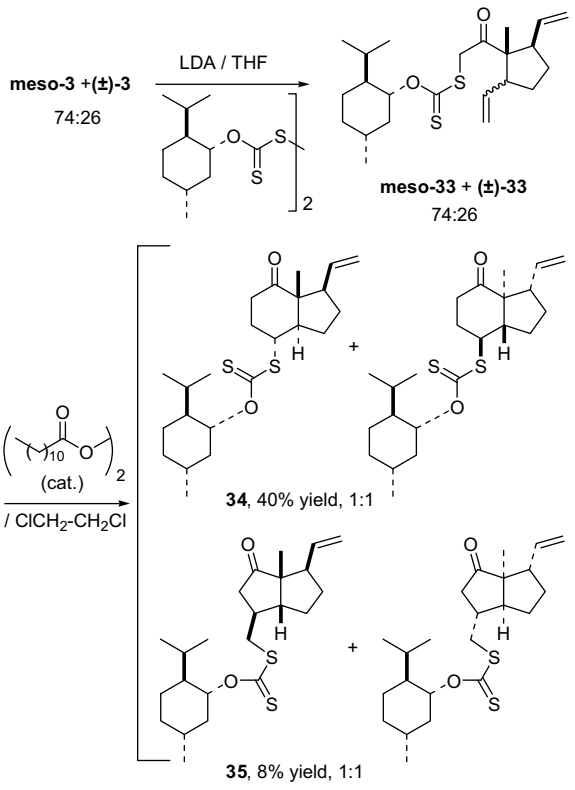
The second strategy involved cross metathesis reaction of the vinyl group of **16** or **28** and the allyltrimethylsilane.[46] Reaction with 2 mol % of Grubbs second generation catalyst gave the cross-metathesis products **31** or **32** with a trans C–C double bond in moderate yields (Scheme 17).



Scheme 17. Functionnalization of the vinyl group by cross-metathesis.

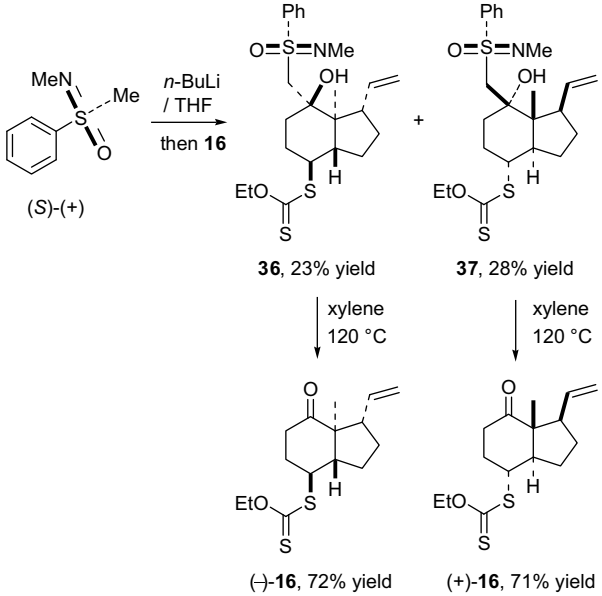
Access to the key building block **16** in an enantiomerically pure form was also studied. First, bis[(−)-menthyl(thiocarbonyl)]-disulfide was used instead of diethyl bis-xanthate to quench the lithium enolate mixture of *anti-meso*-**3** and (±)-**3** (74:26) (Scheme 18).[47] Unfortunately, the diastereomeric mixture of hydrindanes **34**, resulting from the group transfer radical cyclisation process and isolated as the major product, proved to be inseparable by flash column chromatography on silica gel. An attempt with the bis[(*S*)-2-(*N*-tosylpyrrolidinemethyl)(thiocarbonyl)] disulfide, prepared from (*S*)-(+)-prolinol,[48] led to the corresponding diastereomeric mixture of hydrindanes in poor yield and which showed the same problem of separation.

As enantioselective cyclizations of chiral substrates did not look optimistic, we used the sulfoximine ketone resolution methodology developed by Johnson and co-workers[49,50] that should allow us to access to both enantiomers of **16**. Addition of the lithio derivative of (*S*)-(+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine[51] to *rac*-**16** in THF at −78 °C gave rise to the two diastereoisomers **36** and **37**, of which the separation by flash column chromatography has been



Scheme 18. Preparation of dithioxanthates **33** and their radical cyclizations.

performed by eluting with a mixture solvent hexane/CH_2Cl_2/AcOEt (60:37:3) (Scheme 19). Adducts **36** (23%) and **37** (28%) were isolated in excellent yield with traces (<5%) of another stereoisomer. The absolute configuration of the diastereomer **36** has been determined by crystallographic X-ray analysis which shown that the 'natural' configuration fitted to **37** (Fig. 4). Thermolysis of the separated adducts **36** and **37** by heating in xylene led to optically pure hydrindanones (−)-**16** or (+)-**16**. The enantiomeric excesses were determined by HPLC (Chiralcel OD-H), and found equal to 99.6% for (−)-**16** and 98.3% for (+)-**16**.



Scheme 19. Resolution of the hydrindanone **16**.

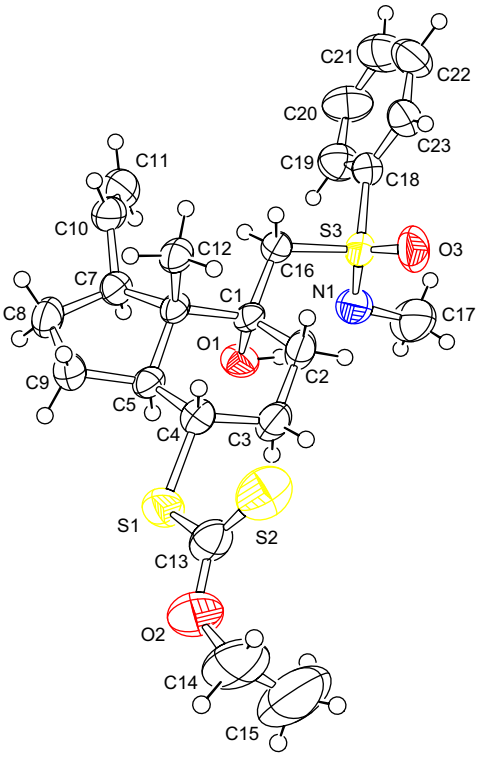


Figure 4. ORTEP diagram of compound **36**.

4. Conclusion

From the easy preparation of epoxyketone **5** and *anti meso* xanthate **13** obtained by desymmetrization of *anti-meso*-acetylmethyldivinylcyclopentane **3**, we have described two expeditious and efficient approaches of versatile *trans*-hydrindanones **7** and **16** respectively, considered as valuable intermediates in the vitamin D derivatives synthesis. A formal enantioselective approach of **7** has also been proposed with the preparation of the enantiomerically enriched compound (+)-**5** involving enantioselective CBS-reduction and diastereoselective bishomoallylic epoxidation as key steps. The Johnson sulfoximine ketone resolution of **16** allowed access to both enantiomers in moderate yield. Functionalizations of the vinyl group revealed as particularly difficult but could be realized by ozonolysis or metathesis favoring the construction of new side chains. Convertion of the xanthate moiety to a benzothiazole-2-sulfonyl (Bts) group allowed the elaboration of an advanced intermediate for Julia–Kociensky coupling. Formation of the trienic part via coupling with elaborated A rings is still underway in our laboratory.

5. Experimental section

5.1. General remarks

THF was freshly distilled from sodium/benzophenone; CH_2Cl_2, triethylamine and pyridine from CaH_2 under N_2. Other reagents and solvents were obtained from commercial sources and used as received. Flash column chromatography: Merck 230–400 mesh silica gel; EtOAc, Et_2O and hexane as eluents. Thin-layer chromatography (TLC): Macherey-Nagel silica gel UV_{254} analytical plates; detection either with UV, or by dipping in a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), KOH (0.3 g) in H_2O (300 mL) and subsequent heating. IR spectroscopy: Perkin–Elmer Paragon 1600 Fourier Transform. NMR spectroscopy: Bruker AC 300 (^{1}H=300 MHz, ^{13}C=75 MHz); chemical shift δ in ppm relative to $CHCl_3$ for ^{1}H (δ=7.26 ppm) and $CDCl_3$ for ^{13}C (δ=77.16 ppm). Carbon–proton couplings were determined by DEPT sequence experiments. Mp: not corrected. Büchi capillary apparatus. Low resolution mass spectra were recorded on a Sciex API III Plus triple quadrupole spectrometer equipped with an electrospray interface, on a Jeol SX 102 spectrometer equipped with a FAB ionisation source (Nitro-Benzyl-Alcohol matrix) and on a Varian Saturn 2100T GC/MS equipped with a WCOT fused silica CP-Sil 8 CB, *m*/*z* (%). High resolution mass spectrometry were measured on a Jeol SX 102 spectrometer equipped with a FAB ionisation source (NBA matrix) to provide accurate mass. Diastereomeric ratios were determined on a Varian 3900 GC equipped with a WCOT fused silica CP Sil 5CB. Enantiomeric ratios were determined on a Shimadzu GC-14A equipped with WCOT fused silica Lipodex-E and Cyclosilb. Optical rotations were measured on a Perkin–Elmer 341 polarimeter.

5.2. 1-Acetyl-1-methyl-2,5-divinylcyclopentane *meso*-3 and (±)-3

Synthesized from 2,2,3,3-tetramethoxybutane and 1,8-bis-(trimethylsilyl)-2,6-octadiene (Bistro) according to the published procedure[13] on 0.8 mol scale, after purification by flash chromatography (hexane/Et_2O, 100:0 to 98:2) the product was obtained as a 74:26 mixture of diastereoisomers *meso*-**3** and (±)-**3** with 47% yield as a yellow oil. ^{1}H NMR *meso*-**3** (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.58–1.71 (m, 2H), 1.88–1.99 (m, 2H), 2.12 (s, 3H), 2.92 (br q, *J*=7.2 Hz, 2H), 5.00 (br d, *J*=17.0 Hz, 2H), 5.01 (br d, *J*=10.7 Hz, 2H), 5.68 (ddd, *J*=16.9, 10.7, 7.8 Hz, 2H); TLC R_f=0.47 (hexane/Et_2O 85:15) (CAS Number: 172337-30-3); ^{1}H NMR (±)-**3** (300 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.50–1.69 (m, 2H), 1.85–2.04 (m, 2H), 2.06 (s, 3H), 2.45 (br q, *J*=7.4 Hz, 1H), 3.20 (br q, *J*=8.3 Hz, 1H), 4.90–5.08 (m, 4H), 5.65 (ddd, *J*=17.0, 10.0, 9.4 Hz, 1H), 5.72 (ddd, *J*=17.3, 10.4, 7.0 Hz, 1H); TLC R_f=0.62 (hexane/Et_2O, 85:15) (CAS Number: 172217-30-0).

5.3. (1*S**,2*R**,5*S**)-1-[(1*S**)-Hydroxyethyl]-1-methyl-2,5-divinylcyclopentane 4

Procedure A. To a stirred solution of *meso*-**3** (1 g, 5.6 mmol) in MeOH (30 mL) was added portionwise $NaBH_4$ (424 mg, 11.2 mmol) at 0 °C. After 4 h stirring at rt, the mixture was hydrolysed with brine (30 mL) and stirred 30 min at rt. The solution was diluted with brine (30 mL) and then extracted with CH_2Cl_2 (4×100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (95:5 30–40 P.E./EtOAc) to provide the racemic compound (±)-**4** (920 mg, 91%) as a colourless oil.

Procedure B. To a stirred molar solution of (*R*)-2-methyl-CBS-oxazaborolidin (0.62 mL, 0.62 mmol) in toluene was slowly added a 1 M solution of BH_3/THF complex (0.56 mL, 0.56 mmol) under argon at rt. A solution of *meso*-**3** (100 mg, 0.56 mmol) in dry toluene (0.5 mL) was added dropwise over 1 min, stirred 10 min and then treated with brine (2 mL) during 30 min. The mixture was diluted with brine (10 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash silica gel chromatography (98:2 30–40 P.E./EtOAc) to provide (+)-(1*S*,2*R*,5*S*)-1-[(1*S*)-hydroxyethyl]-1-methyl-2,5-divinylcyclopentane (+)-**4** (71 mg, 70%; er >99:1 to 97:3; from chiral GC analysis (Lipodex-E column), 100 °C, retention times: 22.72 min for the (1*S*) enantiomer and 24.20 min for the (1*R*) enantiomer) as a colourless oil. $[\alpha]_D^{25}$ +0.1 (*c* 1, $CHCl_3$ for er=97:3); R_f=0.3 (90:10 30–40 P.E./EtOAc); IR 3418, 3075, 2975, 2951, 2873, 1636, 1378, 1000, 911 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.16 (d, *J*=6.5 Hz, 3H), 1.47–1.62 (m, 2H), 1.70–1.82 (m, 2H), 1.86 (br s, 1H),

2.48–2.58 (m, 2H), 3.60–3.68 (m, 1H), 4.95–5.07 (m, 4H), 5.73–5.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 18.5, 28.9, 29.1, 49.7, 51.2, 51.9, 74.5, 115.3, 115.4, 140.4, 140.9; MS (FAB^-) m/z 179 ($[M-H]^-$).

5.4. (1*R**,2*R**,5*R**)-1-[(1*S**)-Hydroxyethyl]-1-methyl-2-[(1*R**)-oxiranyl]-5-vinylcyclopentane 8a and (1*S**,2*S**,5*S**)-1-[(1*S**)-hydroxyethyl]-1-methyl-2-[(1*S**)-oxiranyl]-5-vinylcyclopentane 8b

To a stirred solution of $VO(acac)_2$ (95 mg, 0.36 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise a solution of **4** (640 mg, 3.56 mmol) in dry CH_2Cl_2 (15 mL) under argon at rt. After 15 min stirring was slowly added a 5 M *tert*-butylhydroperoxide/nonane solution (1.06 mL, 5.32 mmol) and the resulting solution was stirred 16 h at 15 °C. The yellow mixture was quenched with a saturated $Na_2S_2O_3$ solution (30 mL) and was stirred 30 min at rt. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The yellow oil obtained was purified by flash silica gel chromatography (90:10 30–40 P.E./EtOAc) to provide a mixture [dr=88:12 at 15 °C from GC analysis, 80 °C/1 min to 260 °C (5 °C/1 min), retention times: 15.62 min for the minor isomer **8b** and 15.82 min for the major isomer **8a**, and 82:18 at T=25 °C from chiral GC analysis (Cyclosilb column), 150 °C, retention times: 21.42 min for **8b** (both enantiomers) and 22.82 min for the (1*S*) enantiomer of **8a** and 23.41 for the (1*R*) enantiomer of **8a**] of two diastereoisomers **8a** and **8b** as a colourless oil (301 mg, 43%, corrected yield 63%) with a recovered amount of starting material (204 mg, 32%). R_f=0.3 (80:20 30–40 P.E./EtOAc); IR (mixture of isomers) 3459, 3074, 3048, 2973, 2873, 1735, 1637, 1473, 1449, 1415, 1402, 1379, 1259, 1063, 1001, 919, 872 cm^{-1}; for the major isomer **8a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.15 (d, J=6.5 Hz, 3H), 1.51–1.63 (m, 2H), 1.71–1.81 (m, 2H), 2.34–2.43 (m, 1H), 2.56 (dd, J=4.5, 3.0 Hz, 1H), 2.84–2.90 (m, 2H), 2.94 (br s, 1H), 3.54 (q, J=6.5 Hz, 1H), 4.95–5.01 (m, 2H), 5.77 (dt, J=18.0, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 18.4, 25.8, 29.8, 48.7, 51.5, 51.9, 52.2, 52.7, 75.1, 115.5, 139.7; MS (FAB^+) m/z 197 ($[M+H]^+$). Representative signals for the minor isomer **8b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.14 (d, J=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 17.9, 24.7, 28.3, 46.5, 48.8, 50.7, 51.8, 52.6, 72.6, 115.8, 139.0.

5.5. (1*R**,2*R**,5*R**)-1-Acetyl-1-methyl-2-[(1*R**)-oxiranyl]-5-vinylcyclopentane 5

To stirred solution of racemic isomers **8a** and **8b** (120 mg, 0.61 mmol) in CH_2Cl_2 (6 mL) was added Dess–Martin periodinane (312 mg, 0.73 mmol) in one portion at rt. The reaction was monitored by TLC analysis. After completion (1 h), the solution was quenched with a saturated $Na_2S_2O_3$ solution (6 mL) and a saturated $NaHCO_3$ solution (6 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (90:10 30–40 P.E./EtOAc) to provide the single product **5** as a colourless oil (118 mg, >99%). R_f=0.5 (80:20 30–40 P.E./EtOAc); IR 3077, 3050, 2980, 2956, 2876, 1698, 1639, 1421, 1355, 1239, 917, 874 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.51–1.73 (m, 2H), 1.82–1.97 (m, 2H), 2.06–2.15 (m, 1H), 2.17 (s, 3H), 2.46 (dd, J=5.0, 2.5 Hz, 1H), 2.73 (dd, J=5.0, 4.0 Hz, 1H), 2.80 (ddd, J=8.0, 4.0, 2.5 Hz, 1H), 2.84–2.93 (m, 1H), 4.96–5.01 (m, 2H), 5.65 (ddd, J=17.0, 10.5, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 24.9, 26.9, 27.9, 47.2, 51.2, 52.1, 52.4, 60.6, 116.6, 137.1, 212.8; HRMS (FAB^+) calculated for $C_{12}H_{19}O_2$ ($[M+H]^+$): 195.1385, found: 195.1397.

For compound (+)-**5**: $[\alpha]_D^{25}$ +14.5 (*c* 0.6, $CHCl_3$). (+)-**5** was obtained from the epoxidation of (+)-**4** (synthesized with a 97:3 er) leading to the chiral mixture of epoxyalcohols **8a**/**8b** with a 82:18 dr, which was oxidized immediately. All attemps made to separate both enantiomers of the resulting epoxyketones on chiral GC so as to measure the enantiomeric ratio (er) were unfruitful. The enantiomeric ratio (er) can be calculated from the er values of (+)-8 and the dr values obtained for **8a**/**8b**, er=((0.97×82)+(0.03×18)):((0.97×18)+(0.03×82))=80:20.

5.6. (1*R**,2*R**,5*R**)-1-[(1*S**)-(3,5-Dinitrobenzoyloxyethyl)]-1-methyl-2-[(1*R**)-(3,5-dinitrobenzoyloxy)-2-iodoethyl]-5-vinylcyclopentane 9

To a stirred solution of **8a** and **8b** (50 mg, 0.25 mmol) in wet MeCN (2.5 mL) was first added NaI (39 mg, 0.26 mmol) followed by $CeCl_3 \cdot 7H_2O$ (95 mg, 0.25 mmol) at rt. The solution was stirred 16 h in the dark and quenched with a saturated $Na_2S_2O_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide a colourless oil (84 mg, >99%). The residue obtained (60 mg) was diluted with dry CH_2Cl_2 (1 mL) and then added to a stirred solution of dry pyridine (1 mL, 12.3 mmol) containing 3,5-dinitrobenzoyl chloride (215 mg, 0.94 mmol). The solution was stirred 3 days under argon at rt and diluted with EtOAc (10 mL). The organic layer was successively washed with a saturated $CuSO_4$ solution (4×5 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude solid obtained was purified by flash silica gel chromatography (95:5 30–40 P.E./EtOAc) to provide the white crystalline compound as an inseparable mixture (in the same relative ratio of the starting material) of two diastereoisomers (130 mg, 99% over two steps). The mixture was crystallised from Et_2O to afford the major product (±)-**13** as a single product. Mp=99–100 °C; R_f=0.6 (95:5 30–40 P.E./EtOAc); IR 3100, 2980, 1733, 1652, 1547, 1345, 1265, 1169, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.38–1.48 (m, 1H), 1.62–1.75 (m, 1H), 1.65 (d, J=6.5 Hz, 3H), 1.98 (m, 2H), 2.67 (dd, J=19.0, 10.0 Hz, 1H), 3.02 (dd, J=19.0, 8.5 Hz, 1H), 3.40 (dd, J=11.5, 2.5 Hz, 1H), 3.76 (dd, J=11.5, 3.0 Hz, 1H), 4.68 (dt, J=10.5, 2.5 Hz, 1H), 5.24 (br d, J=17.0 Hz, 1H), 5.36 (br d, J=10.0 Hz, 1H), 5.49 (q, J=6.5 Hz, 1H), 5.96 (dt, J=17.0, 10.0 Hz, 1H), 9.03 (d, J=2.0 Hz, 2H), 9.16 (t, J=2.0 Hz, 1H), 9.24 (d, J=2.0 Hz, 2H), 9.34 (t, J=2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0, 14.0, 14.1, 24.8, 27.9, 48.5, 48.6, 50.1, 74.7, 78.4, 116.0, 122.4, 123.2, 129.7 (2C), 129.8 (2C), 132.9, 134.0, 138.9, 148.7 (2C), 148.9 (2C), 161.5, 162.2; MS (ESI^+) m/z 730.2 ($[M+NH_4]^+$).

5.7. (1*R**,2*R**,5*R**)-1-Acetyl-1-methyl-2-[(1*R**)-hydroxy-2-iodoethyl]-5-vinylcyclopentane 10

To a stirred solution of **5** (300 mg, 1.54 mmol) in wet MeCN (15 mL) was first added NaI (464 mg, 3.08 mmol) and then $CeCl_3.7H_2O$ (575 mg, 1.54 mmol) at rt. The solution was stirred 16 h in the dark at RT and then quenched with a saturated $Na_2S_2O_3$ solution (15 mL). The mixture was extracted with CH_2Cl_2 (4×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash silica gel chromatography (90:10 30–40 P.E./EtOAc) to provide the white crystalline compound **10** (453 mg, 91%). **10** could be used in the next step without purification. Mp=113–115 °C; R_f=0.4 (80:20 30–40 P.E./EtOAc); IR 3447, 3369, 2953, 2873, 1685, 1360, 1224, 1023, 924 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.58–1.71 (m, 1H), 1.77–1.99 (m, 3H), 2.16 (s, 3H), 2.18–2.21 (m, 1H), 2.64 (dd, J=19.0, 9.5 Hz, 1H), 2.75 (dd, J=19.0, 8.0 Hz, 1H), 3.15–3.26 (m, 2H), 3.44 (dd, J=9.5, 8.0 Hz, 1H), 4.94–5.05 (m, 2H), 5.67 (ddd, J=17.0, 10.5, 8.0 Hz, 1H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 11.1, 17.1, 25.1, 27.3, 28.0, 53.4, 53.6, 60.1, 71.8, 116.8, 136.9, 214.5; MS (FAB^+) m/z 323 ($[M+H]^+$).

5.8. (1*R**,2*R**,5*R**)-1-Acetyl-1-methyl-2-[(1*R**)-tetrahydropyranyloxy-2-iodoethyl]-5-vinylcyclopentane 11

To a stirred solution of **10** (500 mg, 1.55 mmol) in CH_2Cl_2 (15 mL) was added a catalytic amount of *p*-TSA (15 mg, 0.08 mmol) and 3,4-dihydro-2*H*-pyran (0.70 mL, 7.75 mmol). After 30 min stirring at rt, the solution was treated with a saturated $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (98:2 30–40 P.E./EtOAc) to provide an inseparable mixture [dr=50:50 from ^1H NMR determination] of two diastereoisomers **11** (631 mg, >99%) as a white waxy solid. R_f=0.7 (80:20 30–40 P.E./EtOAc); IR 2943, 2869, 1697, 1651, 1455, 1436, 1370, 1123, 1022, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) of the mixture δ: 0.87 (s, 3H, one ds), 1.02 (s, 3H, one ds), 1.15–1.32 (m, 2H, two ds), 1.48–1.57 (m, 8H, two ds), 1.60–1.70 (m, 5H, two ds), 1.80–2.07 (m, 5H, two ds), 2.20 (s, 3H, one ds), 2.21 (s, 3H, one ds), 2.70–2.91 (m, 5H, two ds), 3.01 (ddd, *J*=10.0, 3.0, 1.5 Hz, 1H, one ds), 3.16 (dd, *J*=11.5, 1.5 Hz, 1H, one ds), 3.25 (dd, *J*=10.5, 1.5 Hz, 1H, one ds), 3.40–3.56 (m, 2H, two ds), 3.57 (dd, *J*=11.5, 3.0 Hz, 1H, one ds), 3.73–3.81 (m, 1H, one ds), 3.78 (dd, *J*=10.5, 3.0 Hz, 1H, one ds), 3.99–4.06 (m, 1H, one ds), 4.60 (br s, 2H, two ds), 4.92 (br d, *J*=17.0 Hz, 2H, two ds), 4.99 (br d, *J*=10.5 Hz, 2H, two ds), 5.56 (ddd, *J*=17.0, 10.5, 7.5 Hz, 1H, one ds), 5.58 (ddd, *J*=17.0, 10.0, 7.0 Hz, 1H, one ds); ^{13}C NMR (75 MHz, $CDCl_3$) of the mixture δ: 10.4, 10.9, 11.4, 16.4, 19.1, 19.4, 24.3, 24.4, 24.9, 25.3, 25.4, 25.5, 27.3, 27.4, 29.9, 30.6, 51.6, 52.2, 52.6, 53.8, 59.4, 59.8, 63.2, 63.5, 70.3, 78.4, 94.0, 101.4, 116.3, 116.5, 136.5, 136.8, 211.2, 211.5; HRMS (FAB^+) calculated for $C_{17}H_{28}IO_3$ ($[M+H]^+$): 407.1083, found: 407.1089.

5.9. (1*R**,5*S**,6*R**,9*R**)-1-Methyl-5-tetrahydropyranyloxy-9-vinylbicyclo[4.3.0]nonan-2-one 12

To a stirred solution of **11** (631 mg, 1.55 mmol) in dry THF (20 mL) was added dropwise a 20 wt % THF solution of potassium *tert*-butoxide (1.25 mL, 2.01 mmol) at 50 °C and then stirred 30 min. After completion, the mixture was cooled to rt and quenched with a saturated $Na_2S_2O_3$ solution (20 mL). The mixture was then diluted with brine (20 mL) and extracted with CH_2Cl_2 (4×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yellow crude was purified by flash silica gel chromatography (95:5 30–40 P.E./EtOAc) to afford an inseparable mixture [dr=50:50 from ^1H NMR determination] of two diastereoisomers **12** (432 mg, 89%) as a yellow oil. R_f=0.6 (80:20 30–40 P.E./EtOAc); IR 2940, 2873, 1710, 1456, 1351, 1199, 1126, 1022, 988, 908, 870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) of the mixture δ: 1.16 (s, 3H, one ds), 1.17 (s, 3H, one ds), 1.52–1.93 (m, 23H, two ds), 1.96–2.16 (m, 3H, two ds), 2.24 (ddt, *J*=16.5, 8.5, 2.0 Hz, 1H, one ds), 2.37 (ddt, *J*=16.5, 9.0, 2.5 Hz, 1H, one ds), 2.65–2.75 (m, 2H, two ds), 2.82 (td, *J*=14.0, 6.5 Hz, 1H, one ds), 2.94 (td, *J*=14.0, 6.5 Hz, 1H, one ds), 3.49–3.58 (m, 2H, two ds), 3.85–3.95 (m, 2H, two ds), 3.96 (br s, 1H, one ds), 4.12 (dd, *J*=5.5, 2.5 Hz, 1H, one ds), 4.63 (br t, *J*=3.0 Hz, 1H, one ds), 4.78 (br t, *J*=2.5 Hz, 1H, one ds), 5.04–5.12 (m, 4H, two ds), 5.95 (ddd, *J*=16.5, 11.0, 2.5 Hz, 1H, one ds), 5.97 (ddd, *J*=17.0, 11.0, 3.0 Hz, 1H, one ds); ^{13}C NMR (75 MHz, $CDCl_3$) of the mixture δ: 14.8, 14.9, 19.2, 19.8, 22.1, 22.3, 24.2, 24.3, 25.6, 25.7, 31.1, 31.3 (2C), 34.5, 34.7, 35.1, 46.7, 46.9, 53.6, 53.8, 56.2, 56.3, 61.8, 62.8, 69.4, 75.0, 94.9, 101.3, 115.2, 115.3, 139.1, 139.2, 215.3, 215.5; MS (FAB^+) m/z 279 ($[M+H]^+$).

5.10. (1*R**,5*S**,6*R**,9*R**)-1-Methyl-5-hydroxy-9-vinylbicyclo[4.3.0]nonan-2-one 7

To a stirred solution of **12** (91 mg, 0.33 mmol) in MeOH/H_2O (2 mL, 2:1) was added *p*-TSA (70 mg, 0.36 mmol) at rt and the solution was stirred for 18 h. The solution was then diluted with EtOAc (50 mL), washed with a saturated $NaHCO_3$ solution (2×20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash silica gel chromatography (80:20 30–40 P.E./EtOAc) to afford the single product **7** as a white solid (63 mg, >99%) which was crystallised from hexane. Mp=67–68 °C; R_f=0.3 (70:30 30–40 P.E./EtOAc); IR 3447, 3055, 2961, 2879, 1703, 1265, 738, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.57–1.97 (m, 6H), 2.03 (br s, 1H), 2.09 (ddd, *J*=14.0, 5.5, 2.5 Hz, 1H), 2.16 (ddt, *J*=14.5, 6.5, 2.5 Hz, 1H), 2.67 (ddd, *J*=14.5, 8.5, 6.0 Hz, 1H), 2.94 (td, *J*=14.5, 6.5 Hz, 1H), 4.17 (br s, 1H), 5.04 (dt, *J*=11.0, 2.0 Hz, 1H), 5.05 (dt, *J*=16.5, 2.0 Hz, 1H), 5.93 (ddd, *J*=16.5, 11.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 21.9, 24.1, 34.4, 35.7, 46.6, 53.7, 56.0, 67.2, 115.3, 138.8, 215.5; MS (FAB^+) m/z 195 ($[M+H]^+$).

5.11. 1-Trimethylsilyloxyvinyl-1-methyl-2,5-divinylcyclopentane *meso*-14 and/or (±)-14

General procedure 1. To a solution of divinylcyclopentane *meso*-**3** (500 mg, 2.8 mmol) in anhydrous CH_2Cl_2 (51 mL) at 0 °C under argon was added diisopropylethylamine (2.94 mL, 16.9 mmol), followed by TMSOTf (2.03 mL, 11.2 mmol). The resulting yellow mixture was stirred at 0 °C under argon for 2 h before it was quenched with satd $NaHCO_3$ solution and diluted with hexane. The organic layer was separated and the aqueous layer extracted with hexane. The combined organic extracts were dried over K_2CO_3, filtered, and concentrated in vacuo to afford the crude TMS/silyl enol ether *meso*-**14** (700 mg, 100% yield) as a yellow oil. The crude product was not purified nor submitted to NMR analysis but directly used in the next reaction without further purification. (±)-**14**. Prepared from the divinylcyclopentane (±)-**3** (500 mg, 2.8 mmol) according to the previous general procedure. The crude TMS/silyl enol ether (±)-**14** was obtained with quantitative yield as a yellow oil. Mixture of *meso*-**14** and (±)-**14**. Prepared from a 74:26 mixture of divinylcyclopentanes *meso*-**3** and (±)-**3** (10 g, 56 mmol) following the general procedure. The mixture of TMS-silyl enol ethers **14** was obtained with quantitative yield (14 g) as a yellow oil.

5.12. 1-Bromoacetyl-1-methyl-2,5-divinylcyclopentane 15. *meso*-15

General procedure 2. To a stirred solution of TMS-enol ether *meso*-**14** (700 mg, 2.8 mmol) in 60 mL of anhydrous THF at −78 °C was added $NaHCO_3$ powder (282 mg, 3.4 mmol), followed by the addition of NBS (598 mg, 3.4 mmol) in one portion. The resulting reaction was stirred at −78 °C for 3 h and quenched with a satd $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography eluting with hexane/Et_2O (95:5) to afford the desired product *meso*-**15** (484 mg, 1.9 mmol, 67%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.73–1.62 (m, 2H), 2.02–1.90 (m, 2H), 2.97 (br q, *J*=6.8 Hz, 2H), 4.11 (s, 2H), 5.04 (br d, *J*=16.8 Hz, 2H), 5.05 (br d, *J*=10.6 Hz, 2H), 5.69 (ddd, *J*=16.8, 10.6, 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 27.8 (2C), 34.7, 52.3 (2C), 62.0, 117.1 (2C), 137.3 (2C), 204.3; IR 2952, 1718, 1637, 1386, 999, 919 cm^{-1}; TLC R_f=0.52 (hexane/Et_2O, 95:5) (CAS Number: 886840-75-1). (±)-**15** prepared from TMS/enol ether (±)-**14** (700 mg, 2.8 mmol) according to the general procedure 2. After purification by flash chromatography, the desired product (±)-**3** was isolated as a yellow oil (491 mg, 1.9 mmol, 68%). ^1H NMR

(300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.70–1.54 (m, 2H), 2.06–1.89 (m, 2H), 2.48 (br q, J=7.6 Hz, 1H), 3.25 (br q, J=8.3 Hz, 1H), 3.99 ($^1/_2$ AB, J=13.9 Hz, 1H), 4.10 ($^1/_2$ AB, J=13.9 Hz, 1H), 4.97–5.11 (m, 4H), 5.60 (dt, J=16.9, 9.8 Hz, 1H), 5.71 (ddd, J=17.4, 10.3, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 28.5, 30.1, 35.1, 47.6, 56.1, 61.7, 116.0, 116.2, 138.0, 139.0, 203.4; IR 2954, 1716, 1637, 1381, 1002, 917 cm^{-1}; TLC R_f=0.52 (hexane/Et_2O, 95:5) (CAS Number: 886732-18-9). Mixture of *meso*-**15** and (±)-**15**. Prepared from the mixture of TMS-enol ether **14** (14 g, 56 mmol) according to the general procedure 2. After purification by flash chromatography, the desired products were obtained as an inseparable mixture of *meso*-**15** and (±)-**15** in a 74:26 ratio (9.77 g, 38 mmol, 68%). Physical and spectral data were in accordance with the data described below.

5.13. *O*-Ethyl *S*-[2-(1-methyl-2,5-divinylcyclopentyl)-2-oxoethyl] carbonodithioate 13. *meso*-13

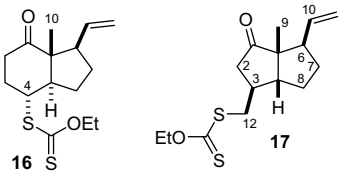
General procedure 3. To a stirred solution of α-bromo ketone *meso*-**15** (484 mg, 1.9 mmol) in 73 mL of acetone at rt under argon was added portionwise 2.33 g (14.6 mmol) of KSC(S)OEt. The resulting reaction was stirred for 2 h at rt until it was diluted with ether and washed with a satd solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/Et_2O, 95:5) to give 392 mg (1.3 mmol, 68%) of a yellow oil. *meso*-**13**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.41 (t, J=7.1 Hz, 3H), 1.65–1.75 (m, 2H), 1.91–2.03 (m, 2H), 3.02 (q, J=7.1 Hz, 2H), 4.24 (s, 2H), 4.63 (q, J=7.1 Hz, 2H), 5.04 (br d, J=16.6 Hz, 2H), 5.05 (br d, J=10.7 Hz, 2H), 5.73 (ddd, J=16.6, 10.7, 7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 13.8, 27.7 (2C), 45.0, 52.0 (2C), 61.7, 70.4, 116.8 (2C), 137.4 (2C), 205.8, 213.8; IR 2978, 1700, 1639, 1472, 1382, 1228, 1112, 1051, 918 cm^{-1}; TLC R_f=0.52 (hexane/Et_2O, 95:5) (CAS Number: 886732-15-6). (±)-**13**. Prepared from the α-bromo ketone (±)-**15** (491 mg, 1.9 mmol) according to the general procedure 3. After purification by flash chromatography, the desired product (±)-**13** was isolated as a yellow oil (390 mg, 1.3 mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.41 (t, J=7.1 Hz, 3H), 1.56–1.71 (m, 2H), 1.89–2.08 (m, 2H), 2.51 (br q, J=7.5 Hz, 1H), 3.24 (br, q, J=8.1 Hz, 1H), 4.03 ($^1/_2$ AB, J=17.3 Hz, 1H), 4.36 ($^1/_2$ AB, J=17.3 Hz, 1H), 4.63 (q, J=7.1 Hz, 2H), 4.94–5.10 (m, 4H), 5.63 (dt, J=16.9, 9.8 Hz, 1H), 5.71 (ddd, J=17.4, 10.3, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 19.8, 28.5, 30.1, 45.9, 47.5, 56.1, 61.4, 70.5, 115.9, 116.0, 138.3, 139.1, 205.2, 214.0; IR 2976, 1707, 1637, 1458, 1380, 1220, 1113, 1052, 918 cm^{-1}; TLC R_f=0.52 (hexane/Et2O, 95:5); (CAS Number 886840-76-2). Mixture of *meso*-**13** and (±)-**13**. Prepared from the mixture of α-bromo ketone *meso*-**15** and (±)-**15** (9.77 g, 38 mmol) according to the general procedure 3. After purification by flash chromatography, the desired products were obtained as an inseparable mixture of *meso*-**13** and (±)-**13** in a 74:26 ratio (9.1 g, 31 mmol, 82%). Physical and spectral data were in accordance with the data described previously.

5.14. Mixture of *meso*-13 and (±)-13

General procedure 4. To a stirred solution of diisopropylamine (11.9 mL, 85 mmol) in 200 mL of anhydrous THF at −78 °C under argon, was added dropwise a solution of *n*-BuLi 1.6 M in hexane (48.8 mL, 78 mmol) in 50 mL of anhydrous THF. The mixture was stirred 30 min at −78 °C under argon. Then, the 70:30 mixture of divinylcyclopentanes *meso*-**3** and (±)-**3** (12.5 g, 70 mmol) in 50 mL of anhydrous THF was added dropwise at −78 °C and the resulting mixture stirred 1 h at −78 °C under argon. *O*,*O*-Diethyl bis-xanthate in 50 mL of anhydrous THF (34.2 g, 141 mmol), prepared according to the method of Shi and co-workers,[30b] was added dropwise at −78 °C. The reaction was stirred 1 h at −78 °C, then poured in a satd NH_4Cl solution. The layers were then separated and the aqueous layer extracted twice with ether. The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by flash chromatography (hexane/Et_2O, 98:2 to 80:20), the desired products *meso*-**13** and (±)-**13** were obtained as an inseparable mixture in a 70:30 ratio (15.6 g, 52 mmol, 75%). Physical and spectral data were in accordance with the data described previously.

5.15. *O*-Ethyl *S*-[(1*R**,3a*R**,4*R**,7a*R**)-octahydro-7a-methyl-7-oxo-1-vinyl-1*H*-inden-4-yl] carbonodithioate 16, *O*-ethyl *S*-[((3*S**,3a*R**,6*R**,6a*R**)-octahydro-6a-methyl-1-oxo-6-vinylpentalen-3-yl)methyl] carbonodithioate 17 and *O*-ethyl *S*-[(1*S**,3a*R**,4*R**,7a*R**)-octahydro-7a-methyl-7-oxo-1-vinyl-1*H*-inden-4-yl]carbonodithioate 18

General procedure 5. Under argon, 41 mg (0.1 mmol) of lauroyl peroxide (DLP) was added to a refluxing solution containing 392 mg (1.3 mmol) of xanthate *meso*-**13** in 48 mL of anhydrous 1,2-dichloroethane. The reaction was refluxed for 1 h 30 min, and then 0.08 equiv of DLP was further added. After another 1 h 30 min refluxing under argon, the solvent was removed in vacuo. The residue was purified by flash chromatography (hexane/Et_2O, 95:5 to 80:20) to give 271 mg (0.9 mmol, 70%) of **16** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.44 (t, J=7.1 Hz, 3H), 1.60–1.81 (m, 4H), 1.87–1.97 (m, 2H), 2.27 (ddd, J=14.6, 5.8, 1.8 Hz, 1H), 2.56–2.66 (m, 1H), 2.70–2.85 (m, 2H), 4.12 (td, J=11.9, 4.4 Hz, 1H), 4.67 (q, J=7.1 Hz, 1H), 5.08 (dt, J=10.8, 1.6 Hz, 1H), 5.10 (dt, J=16.9, 1.6 Hz, 1H), 5.96 (ddd, J=16.9, 10.8, 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 13.9, 23.9, 24.8, 34.1, 38.0, 46.5, 47.8, 53.3, 57.0, 70.2, 115.7, 138.3, 212.5, 214.0; IR 2954, 1698, 1639, 1454, 1379, 1225, 1047, 914, 810 cm^{-1}; TLC R_f=0.40 (hexane/Et_2O, 90:10). Besides, COSY and NOESY experiments confirmed the stereochemistry. NOESY CH_3-9→H-10. Mixture of **17** and **18**. Prepared from the xanthate (±)-**13** (390 mg, 1.3 mmol) according to the general procedure 5. The reaction was stirred at reflux and further DLP (0.08 equiv) was added after 30 min, 1 h 30 min (0.08 equiv) and 2 h 30 min (0.16 equiv). After 3 h refluxing, the solvent was removed in vacuo. After purification by flash chromatography, 62 mg (0.2 mmol, 16%) of product **18** and 120 mg (0.4 mmol, 31%) of product **17** were isolated as yellow oils. ^{1}H NMR **17** (500 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.43 (t, J=7.1 Hz, 3H), 1.68–1.79 (m, 2H), 1.90–1.95 (m, 1H), 2.08–2.12 (m, 3H), 2.22–2.28 (m, 1H), 2.52 (q, J=8.1 Hz, 1H), 2.72 ($^1/_2$ AB, d, J=18.1, 7.6 Hz, 1H), 3.07 ($^1/_2$ AB, d, J=13.6, 8.5 Hz, 1H), 3.44 ($^1/_2$ AB, d, J=13.6 Hz, 5.2 Hz, 1H), 4.66 (q, J=7.1 Hz, 2H), 4.99 (br d, J=17.3 Hz, 1H), 5.06 (br d, J=10.4 Hz, 1H), 5.75 (ddd, J=17.3, 10.4, 7.1 Hz, 1H); ^{13}C NMR **17** (75 MHz, $CDCl_3$) δ 13.9, 17.5, 29.4, 30.4, 39.8, 40.9, 43.6, 48.7, 56.0, 59.7, 70.4, 116.4, 136.6, 214.5, 218.9; IR **17** 2952, 1732, 1639, 1455, 1372, 1213, 1046, 1003, 915, 863 cm^{-1}; NOESY CH_3-9→H-10, H-6→H-3, H-6→H-7 (α), H-3→H-2 (α), H-12→H-8 (β); TLC **17** R_f=0.29 (hexane/Et_2O, 90:10); ^{1}H NMR **18** (300 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.44 (t, J=7.1 Hz, 3H), 1.60–2.15 (m, 6H), 2.45–2.72 (m, 4H), 3.01 (q, J=8.4 Hz, 1H), 3.82 (td, J=11.1, 3.3 Hz, 1H), 4.67 (q, J=7.1 Hz, 2H), 4.99 (br d, J=17.3 Hz, 1H), 5.04 (br d, J=10.4 Hz, 1H), 5.67 (ddd, J=17.3, 10.4, 7.4 Hz, 1H); ^{13}C NMR **18** (75 MHz, $CDCl_3$) δ 13.9, 18.3, 27.8, 29.4, 31.4, 37.5, 49.6, 51.9, 53.2, 58.8, 70.2, 116.5, 136.8, 212.4, 214.3; IR **18** 2956, 1704, 1640, 1456, 1376, 1215, 1048, 1002, 915, 843 cm^{-1}; TLC **18** R_f=0.40 (hexane/Et_2O, 90:10). Mixture of **16** and **17**. Prepared from the 70:30 mixture of xanthates *meso*-**13** and (±)-**13** (9.1 g, 31 mmol) according to the general procedure 5. The reaction was stirred at reflux and further DLP was added after 2 h (0.08 equiv). After 4 h refluxing, the solvent was removed in vacuo. After purification by flash chromatography, 5.45 g (18 mmol, 59%) of **16**, 1.3 g (4 mmol, 14%) of **17** were isolated as yellow oils and no **18** was observed. Physical and spectral data were in accordance with the data described previously.



5.16. *O*-Ethyl *S*-[(1*R**,3a*R**,4*R**,7a*R**)-octahydro-7a-methyl-7-oxo-1-vinyl-1*H*-inden-4-yl] carbonodithioate ethylene ketal 20

A solution was prepared by refluxing, with a Dean–Stark water trap under argon, a mixture of toluene (295 mL), ethylene glycol (12 mL, 216 mmol) and *p*-TSA (137 mg, 0.72 mmol). Precursor **16** (5.45 g, 18 mmol) was then added and the mixture was refluxed for 5 h. The cooled solution was washed with a satd $NaHCO_3$ solution and water. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/Et_2O, 90:10) to give 5.2 g (15 mmol, 85%) of a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.41 (t, J=7.1 Hz, 3H), 1.45–1.64 (m, 4H), 1.68–1.86 (m, 3H), 1.98 (td, J=7.1, 5.1 Hz, 1H), 2.16–2.25 (m, 1H), 2.71 (q, J=8.5 Hz, 1H), 3.76 (td, J=12.0, 4.3 Hz, 1H), 3.85–4.01 (m, 4H), 4.63 (q, J=7.1 Hz, 2H), 4.67 (q, J=7.1 Hz, 1H), 4.92 (br d, J=16.7 Hz, 1H), 4.94 (br d, J=10.8 Hz, 1H), 5.08 (dt, J=10.8, 1.6 Hz, 1H), 5.10 (dt, J=16.9, 1.6 Hz, 1H), 5.94 (ddd, J=16.7, 10.8, 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 13.9, 25.0, 26.1, 31.1, 32.1, 46.5, 48.7, 49.4, 51.9, 64.7, 65.5, 66.8, 111.9, 113.9, 140.3, 214.8; IR 2955, 1636, 1448, 1381, 1343, 1210, 1048, 1002, 906, 774 cm^{-1}; TLC R_f=0.46 (hexane/Et_2O 90:10); MS (ESI^+) m/z 343.1 ($[M+H]^+$).

5.17. (3*R**,3a*R**,7*R**,7a*R**)-Octahydro-7-mercapto-3a-methyl-3-vinylinden-4-one ethylene ketal 21

Under argon, compound **20** (5.2 g, 15 mmol) was diluted in 13 mL of ethanol at rt. Then, ethylene diamine (4.1 mL, 61.5 mmol) was added dropwise at rt, the mixture was stirred for 4 h at rt under argon and poured on a 2 M H_2SO_4 aqueous solution. The layers were separated and the aqueous layer extracted twice with ether. The organic layers were washed with a 2 M H_2SO_4 aqueous solution, followed by a satd $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The yellow oil obtained (3.43 g, 13.5 mmol, 90%) was not purified and directly used in the next reaction. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.29–1.39 (m, 3H), 1.45–1.61 (m, 5H), 1.69–2.03 (m, 7H), 2.67–2.85 (m, 2H), 3.85–4.00 (m, 4H), 4.92 (br d, J=16.3 Hz, 1H), 4.94 (br d, J=11.2 Hz, 1H), 5.93 (ddd, J=16.3, 11.2, 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 25.6, 25.9, 32.3, 36.1, 37.8, 46.6, 51.4, 54.2, 64.6, 65.4, 112.1, 113.7, 140.4; IR 2952, 2873, 1520, 1170, 1133, 1057, 951, 908 cm^{-1}; TLC R_f=0.83 (hexane/Et_2O, 90:10 eluting two times).

5.18. (3*R**,3a*R**,7*R**,7a*R**)-7-(Benzo[*d*]thiazol-2-ylthio)-octahydro-3a-methyl-3-vinylinden-4-one ethylene ketal 22

Thiol **21** (3.43 g, 13.5 mmol) in 61 mL of anhydrous THF was added to a suspension of 1.62 g of sodium hydride (40.5 mmol) in 21 mL of anhydrous THF at rt under argon. The reaction mixture was stirred at rt for 30 min. Then, a solution of 2-chlorobenzothiazole (5.73 g, 34 mmol), prepared according to the method of Boga and co-workers,[51] in 30 mL of anhydrous THF was added dropwise. The reaction was refluxed overnight. Then, the THF was distilled and the mixture washed with brine and extracted twice with ether. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/Et_2O, 90:10 to 70:30) to give a brown oil crystallizing when cooled to 5–10 °C (3.3 g, 8.5 mmol, 63%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.48–1.91 (m, 7H), 2.01–2.08 (m, 1H), 2.32–2.40 (m, 1H), 2.75 (q, J=8.4 Hz, 1H), 3.87–4.02 (m, 5H), 4.94 (br d, J=16.7 Hz, 1H), 4.96 (br d, J=10.9 Hz, 1H), 5.96 (ddd, J=16.7, 10.9, 7.3 Hz, 1H), 7.29 (td, J=7.7, 1.2 Hz, 1H), 7.41 (td, J=7.4, 1.2 Hz, 1H), 7.74 (dd, J=7.9, 0.6 Hz, 1H), 7.88 (dd, J=8.1, 0.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 25.3, 26.2, 32.1, 32.2, 46.5, 47.1, 50.6, 52.0, 64.7, 65.5, 77.4, 112.0, 113.9, 121.0, 121.8, 124.3, 126.1, 135.5, 140.3, 153.5, 166.5; IR 3442, 1652, 1625, 1404, 1322, 975, 869, 785 cm^{-1}; TLC R_f=0.27 (hexane/Et_2O, 90:10); mp=118–120 °C.

5.19. (3*R**,3a*R**,7*R**,7a*R**)-7-(Benzo[*d*]thiazol-2-ylsulfonyl)-octahydro-3a-methyl-3-vinylinden-4-one ethylene ketal 23

A stirred suspension of the thioether **22** (3.3 g, 8.5 mmol) in 110 mL of EtOH at 0 °C under argon was treated with ammonium heptamolybdate tetrahydrate (1.05 g, 0.85 mmol) in 35% H_2O_2 (3.64 mL, 42.5 mmol) and the resulting suspension allowed to warm to rt over 1 h. After subsequent stirring at rt for 6 h, further ammonium heptamolybdate tetrahydrate (1.05 g, 0.85 mmol) in 35% H_2O_2 (3.64 mL, 42.5 mmol) was added and the mixture stirred at rt for a further day. Then, the mixture was diluted with ether and water and the layers separated. The aqueous layer was then extracted four times with ether and the combined organic extracts washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The white solid obtained (2.85 g, 6.8 mmol, 80%) was not purified and can be used as well in a subsequent reaction. This compound was recrystallized in a solution ether/CH_2Cl_2 (just a few drops) in order to be characterized by X-ray crystallographic analysis. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.45–1.80 (m, 4H), 1.85–1.95 (m, 3H), 2.04 (br q, J=9.0 Hz, 1H), 2.29 (td, J=11.5, 7.9 Hz, 1H), 2.68 (q, J=8.6 Hz, 1H), 3.62–3.66 (m, 1H), 3.82–3.98 (m, 4H), 4.92 (br d, J=17.5 Hz, 1H), 4.94 (br d, J=10.7 Hz, 1H), 5.89 (ddd, J=17.5, 10.7, 7.3 Hz, 1H), 7.61 (br q, J=7.6 Hz, 2H), 8.0 (dd, J=7.8, 1.1 Hz, 1H), 8.23 (dd, J=8.0, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 24.5, 25.0, 26.8, 30.5, 44.5, 45.3, 52.0, 62.8, 64.8, 65.5, 111.0, 114.3, 122.4, 125.6, 127.7, 128.0, 137.0, 139.7, 153.0, 166.1; IR 3441, 3051, 1652, 1622, 1403, 1320, 1145, 974, 821, 728 cm^{-1}; TLC R_f=0.44 (hexane/Et_2O, 50:50); mp=88–90 °C; MS (ESI^+) m/z 420.4 ($[M+H]^+$).

5.20. *S*-(1*R**,3a*R**,4*R**,7a*R**)-Octahydro-7a-methyl-7-oxo-1-vinyl-1*H*-inden-4-yl benzothioate ethylene ketal 24

To a stirred solution of thiol **21** (1.77 g, 7 mmol) in dry pyridine (10.1 mL) under argon was added dropwise at 0 °C benzoyl chloride (1.61 mL, 14 mmol). The mixture was stirred at rt and after 7 h it was diluted with CH_2Cl_2. The organic phase was washed with water, a satd solution of $NaHCO_3$ and brine. The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue obtained was purified by flash chromatography (hexane/Et_2O, 90:10) to give 55 mg (0.2 mmol, 3%) of starting material **10**, 0.247 g (0.5 mmol, 7%) of disulfide and 1.745 g (4.9 mmol, 66%) of the protected thiol **24** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.35–1.85 (m, 4H), 1.89 ($^1/_2$ AB, d, J=14.9, 4.7 Hz, 1H), 2.01 ($^1/_2$ AB, d, J=12.4, 7.2 Hz, 1H), 2.06–2.15 (m, 3H), 2.74 (q, J=8.4 Hz, 1H), 3.78 (td, J=12.2, 4.2 Hz, 1H), 3.87–4.04 (m, 4H), 4.94 (br d, J=16.7 Hz, 1H), 4.95 (br d, J=10.9 Hz, 1H), 5.96 (ddd, J=16.7, 10.9, 7.4 Hz, 1H), 7.43 (br t, J=7.3 Hz, 2H), 7.54 (br d, J=8.0 Hz, 1H), 7.94 (br d, J=8.4 Hz, 2H); TLC R_f=0.33 (hexane/Et_2O, 90:10).

5.21. *S*-(1*S**,3a*R**,4*R**,7a*R**)-1-Formyl-octahydro-7a-methyl-7-oxo-1*H*-inden-4-yl benzothioate ethylene ketal 25

To a stirred solution of compound **24** (1.6 g, 4.5 mmol), MeOH (1 mL, 24 mmol) and a catalytic amount of dye sudan III (20 mg, 0.056 mmol) in dry CH_2Cl_2 (40 mL) was bubbled a stream of ozone in oxygen at −60 °C until the red color of sudan III became yellow

(25 min). Excess of ozone and oxygen were removed with argon flushed and then ozonide was quenched with Me_2S (5 mL) slowly added at −78 °C. The solution was warmed to rt over 12 h, washed four times with water, dried over $MgSO_4$, filtered and concentrated in vacuo and the residue was purified by flash chromatography (hexane/EtOAc, 75:25) to give 0.94 g (2.6 mmol, 58%) of compound **25** as a yellow oil and 0.130 g (0.3 mmol, 7%) of ozonide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.85–1.95 (m, 6H), 2.02–2.16 (m, 3H), 2.97 (td, J=9.9, 2.3 Hz, 1H), 3.78 (td, J=12.2, 4.3 Hz, 1H), 3.94–4.16 (m, 4H), 7.44 (t, J=7.8 Hz, 2H), 7.56 (t, J=6.9 Hz, 1H), 7.94 (d, J=7.8 Hz, 2H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 19.5, 25.2, 31.0, 31.3, 40.8, 50.4, 53.2, 54.9, 64.6, 65.4, 111.0, 127.1 (2C), 128.6 (2C), 133.3, 137.1, 191.6, 204.3; TLC R_f=0.52 (hexane/EtOAc, 75:25).

5.22. (*E*)-Ethyl 3-((3*R**,3a*R**,7*R**,7a*R**)-octahydro-3a-methyl-7-benzoylsulfanyl-4-oxo-1*H*-inden-3-yl)acrylate ethylene ketal 26

To a stirred solution of sodium hydride (0.042 g, 1.05 mmol) in dry THF (1.5 mL) under argon was added dropwise triethyl phosphonoacetate (0.29 mL, 1.5 mmol) at 0 °C. The mixture was stirred 30 min at rt until the aldehyde **25** (0.360 g, 1 mmol) in 1.4 mL of dry THF was added dropwise at 0 °C and the mixture stirred at rt. After 2 h 30 min, the reaction mixture was quenched with a satd NH_4Cl solution and the aqueous layer extracted twice with ether. The residue was purified by flash chromatography (hexane/EtOAc, 75:25) to give 0.168 g (0.39 mmol, 39%) of compound **26** as a colorless oil and 0.074 g (0.21 mmol, 21%) of starting material **25**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.40–1.90 (m, 5H), 2.02–2.14 (m, 4H), 2.89 (q, J=8.5 Hz, 1H), 3.78 (td, J=12.2, 4.4 Hz, 1H), 3.84–4.04 (m, 4H), 4.18 (q, J=7.1 Hz, 2H), 5.73 (dd, J=15.6, 1.2 Hz, 1H), 7.09 (dd, J=15.7, 7.8 Hz, 1H), 7.44 (t, J=7.5 Hz, 2H), 7.56 (t, J=7.4 Hz, 1H), 7.94 (d, J=8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 14.4, 25.2, 25.9, 31.7, 41.7, 45.3, 50.1, 52.6, 60.2, 64.6, 65.3, 111.6, 120.7, 127.3 (2C), 128.6 (2C), 133.4, 137.3, 151.0, 166.8, 191.9; TLC R_f=0.61 (hexane/EtOAc, 75:25).

5.23. (3*R**,3a*R**,7*R**,7a*R**)-Octahydro-7-mercapto-3a-methyl-3-vinylinden-4-one 27

Prepared from precursor **16** (4.3 g, 14 mmol) in EtOH (15.5 mL) and ethylene diamine (4.82 mL, 72 mmol) following the general procedure described for thiol **21**. The yellow oil obtained after workup (3 g, 14 mmol, 100%) was not purified and directly used in the next reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.44–1.88 (m, 5H), 1.96–2.06 (m, 1H), 2.22 ($^1/_2$ AB, dd, J=14.6, 5.8, 1.8 Hz, 1H), 2.70 (ddd, J=14.4, 13.8, 7.0 Hz, 1H), 2.38 (dddd, J=13.3, 6.9, 4.3, 1.8 Hz, 1H), 2.82 (qm, J=8.2, 1H), 3.17 (tdd, J=11.4, 6.6, 4.4 Hz, 1H), 5.08 (dt, J=10.7, 1.8 Hz, 1H), 5.09 (dt, J=17.0, 1.8 Hz, 1H), 5.94 (ddd, J=17.0, 10.7, 5.8 Hz, 1H); TLC R_f=0.33 (hexane/Et_2O, 90:10).

5.24. *S*-(1*R**,3a*R**,4*R**,7a*R**)-Octahydro-7a-methyl-7-oxo-1-vinyl-1*H*-inden-4-yl benzothioate 28

Prepared from precursor **27** (3 g, 14 mmol) in dry pyridine (20 mL) and dry benzoyl chloride (3.28 mL, 28 mmol) according to the general procedure described for precursor **24**. After 7 h stirring at rt, the mixture was treated as described below and the residue obtained was purified by flash chromatography (hexane/Et_2O, 90:10) to give 3.27 g (10.4 mmol, 74%) of the protected thiol **28** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.55–2.01 (m, 6H), 2.29 ($^1/_2$ AB, dd, J=14.5, 5.7, 1.7 Hz, 1H), 2.45–2.54 (m, 1H), 2.77–2.89 (m, 2H), 4.12 (td, J=12.0, 4.5 Hz, 1H), 5.09 (br d, J=10.7, 1.6 Hz, 1H), 5.11 (br dt, J=17.0, 1.6 Hz, 1H), 5.97 (ddd, J=17.0, 10.7, 5.9 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.56 (t, J=7.8 Hz, 1H), 7.95 (d, J=7.6 Hz, 2H); TLC R_f=0.29 (hexane/Et_2O, 90:10).

5.25. *S*-(1*S**,3a*R**,4*R**,7a*R**)-1-Formyl-octahydro-7a-methyl-7-oxo-1*H*-inden-4-yl benzothioate 29

To a stirred solution of compound **28** (0.314 g, 1 mmol), MeOH (0.22 mL, 5.3 mmol) and a catalytic amount of dye sudan III (5 mg, 0.014 mmol) in dry CH_2Cl_2 (29 mL) according to the procedure described for **19**. The residue was purified by flash chromatography (hexane/EtOAc, 85:15) to give 0.200 g (0.63 mmol, 63%) of compound **29** as a yellow oil and 0.032 g (0.09 mmol, 9%) of ozonide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.55–1.72 (m, 2H), 1.80–2.20 (m, 6H), 2.38–2.56 (m, 4H), 2.84 (td, J=14.0, 7.0 Hz, 1H), 3.18 (t, J=9.1 Hz, 1H), 4.06–4.15 (m, 2H), 7.46 (t, J=7.6 Hz, 2H), 7.59 (t, J=7.4 Hz, 1H), 7.94 (d, J=7.6 Hz, 2H), 9.91 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.6, 18.2, 24.7, 34.1, 37.5, 39.9, 54.1, 55.6, 57.1, 127.2 (2C), 128.7 (2C), 133.6, 136.7, 190.9, 202.1, 211.3; TLC R_f=0.33 (hexane/EtOAc, 85:15).

5.26. (*E*)-Ethyl 3-((3*R**,3a*R**,7*R**,7a*R**)-octahydro-3a-methyl-7-benzoylsulfanyl-4-oxo-1*H*-inden-3-yl)acrylate 30

To a stirred suspension of sodium hydride (0.042 g, 1.05 mmol) in dry THF (1.5 mL) under argon was added dropwise triethyl phosphonoacetate (0.21 mL, 1.05 mmol) at 0 °C. The mixture was stirred 30 min at rt until the aldehyde **29** (0.316 g, 1 mmol) in 1.4 mL of dry THF was added dropwise at 0 °C and the mixture stirred at rt. After 1 h, the reaction mixture was quenched with a satd NH_4Cl solution and the aqueous layer extracted twice with ether. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to give a yellow residue which was purified by flash chromatography (hexane/EtOAc, 75:25) to give 0.185 g (0.48 mmol, 48%) of compound **30** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.62–2.02 (m, 6H), 2.31 (ddd, J=14.4, 5.5, 1.6 Hz, 1H), 2.49 (br quint. J=6.7 Hz, 1H), 2.83 (sext, J=7.1 Hz, 1H), 2.99 (q, J=8.1 Hz, 1H), 4.14 (td, J=7.5, 3.2, 1H), 4.18 (q, J=7.1 Hz, 2H), 5.91 (dd, J=15.8, 1.3 Hz, 1H), 7.05 (dd, J=15.8, 6.5 Hz, 1H), 7.46 (t, J=7.6 Hz, 2H), 7.59 (t, J=7.3 Hz, 1H), 7.94 (d, J=8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 14.2, 24.2, 24.9, 34.5, 37.7, 40.5, 45.5, 54.0, 57.5, 60.1, 122.5, 127.2 (2C), 128.6 (2C), 133.6, 136.8, 148.5, 166.5, 191.1, 211.7; TLC R_f=0.60 (hexane/EtOAc, 75:25).

5.27. *S*-[(1*R**,3a*R**,4*R**,7a*R**)-Octahydro-7a-methyl-1-((*E*)-3-(trimethylsilyl)prop-1-enyl)-7-oxo-1*H*-inden-4-yl] benzothioate 31

Precursor **16** (0.298 g, 1 mmol) in allyltrimethylsilane (0.48 mL, 3 mmol) was stirred at 40 °C under argon in a round bottom flask equipped with a reflux condenser. Second-generation Grubbs' catalyst (0.017 g, 0.02 mmol) was added and the mixture stirred at 40 °C. A second portion of catalyst was added after 6 h and a third portion after 24 h (0.02 equiv each time). After 48 h the mixture was concentrated in vacuo to afford a brown residue which was purified by flash chromatography (hexane/Et_2O, 90:10) to give 0.091 g (0.24 mmol, 24%) of cross-metathesis product **31** as a yellow oil and 0.131 g (0.44 mmol, 44%) of starting product **16**. ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.04 (s, 9H), 1.04 (s, 3H), 1.42 (t, J=7.1 Hz, 3H), 1.61–1.90 (m, 8H), 2.23 ($^1/_2$ AB, dd, J=14.5, 5.7, 1.8 Hz, 1H), 2.53–2.62 (m, 1H), 2.68–2.79 (m, 2H), 4.09 (td, J=11.8, 4.3 Hz, 1H), 4.64 (q, J=7.1 Hz, 2H), 5.30 ($^1/_2$ AB, d, J=15.4 Hz, 6.4 Hz, 1H), 5.48 ($^1/_2$ AB, td, J=15.4, 7.9, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.8 (3C), 13.0, 13.9, 23.1, 24.9, 25.3, 34.1, 38.0, 46.0, 47.9, 53.2, 57.2, 70.0, 127.97, 128.04, 212.5, 214.0; TLC R_f=0.60 (hexane/Et_2O, 90:10).

5.28. *O*-Ethyl *S*-[(1*R**,3a*R**,4*R**,7a*R**)-octahydro-7a-methyl-1-((*E*)-3-(trimethylsilyl)prop-1-enyl)-7-oxo-1*H*-inden-4-yl] carbonodithioate 32

Prepared from compound **28** (0.062 g, 0.2 mmol), allyltrimethylsilane (0.28 mL, 1.8 mmol), second-generation Grubbs' catalyst (3.4 mg, 0.004 mmol) and a few drops of 1,2-dichloroethane according to the procedure described for compound **31**. Both allyltrimethylsilane (3 equiv) and Grubbs'catalyst (0.2 equivt) were added every 12 h and after 4.5 days the mixture was concentrated in vacuo to give a brown residue which was purified by flash chromatography (hexane/Et_2O, 90:10) to give 0.025 g (0.062 mmol, 30%) of cross-metathesis product **32** as a yellow solid and 0.044 g (0.14 mmol, 70%) of starting product **28**. ^1H NMR (300 MHz, $CDCl_3$) δ −0.02 (s, 9H), 1.09 (s, 3H), 1.55–1.60 (m, 2H), 1.44 (d, J=8.0 Hz, 2H), 1.66–2.0 (m, 6H), 2.25 ($^1/_2$ AB, d, J=14.5, 5.7, 1.8 Hz, 1H), 2.44–2.52 (m, 1H), 2.75–2.87 (m, 2H), 4.11 (td, J=12.0, 4.4 Hz, 1H), 5.32 ($^1/_2$ AB, d, J=15.4, 6.4 Hz, 1H), 5.54 ($^1/_2$ AB, td, J=15.6 Hz, 8.0, 1.0, 1 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 7.57 (tt, J=7.4, 1.2 Hz, 1H), 7.97 (d, J=8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.8 (3C), 12.9, 23.1, 25.0, 25.2, 34.9, 38.2, 41.2, 46.1, 54.0, 57.3, 127.4 (2C),128.0, 128.2, 128.8 (2C), 133.6, 137.1, 191.7, 212.9; TLC R_f=0.38 (hexane/Et_2O, 90:10).

5.29. *O*-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl] *S*-2-(1-methyl-2,5-divinylcyclopentyl)-2-oxoethyl carbonodithioate 33. *meso*-33 and (±)-33

Prepared from a mixture of divinylcyclopentane *meso*-**3** and (±)-**3** (2.0 g, 11 mmol) and bis[menthyl(thiocarbonyl)]disulfide (10.18 g, 22 mmol, prepared according to the procedure of Matsui),[46c] according to the general procedure 4. But 1 equiv of bis-[menthyl(thiocarbonyl)disulfide was added first and the mixture stirred for 30 min at −78 °C before the second equivalent was added. After 2 h 10 min at −78 °C, the mixture was quenched with a satd NH_4Cl solution and the aqueous layer extracted twice with ether. The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by flash chromatography (hexane/Et_2O, 100:0 to 80:20), the desired products *meso*-**33** and (±)-**33** were obtained as an inseparable mixture in a 70:30 ratio (2.56 g, 6.3 mmol, 57%) and 36% (0.7 g, 3.9 mmol) of divinylcyclopentane *meso*-**3** and (±)-**3** was recovered. ^1H NMR *meso*-**33** and (±)-**33** (300 MHz, $CDCl_3$) δ 0.78 (d, J=6.9 Hz, 3H), 0.91 (t, J=6.5 Hz, 6H), 1.07 (s, 3H, *meso*-**33**), 1.26 (s, 3H, (±)-**13**), 1.44–1.76 (m, 12H), 2.03–1.81 (m, 8H), 2.22 (br d, J=12.0 Hz, 1H), 2.51 (br q, J=7.5 Hz, 1H, (±)-**33**), 2.96–3.07 (quint, J=7.6 Hz, 2H, *meso*-**33**), 3.20–3.28 (m, 1H, (±)-**33**), 4.04 ($^1/_2$ AB, d, J=17.2, 4.9 Hz, 1H, (±)-**33**), 4.24 (s, 2H, *meso*-**33**), 4.35 ($^1/_2$ AB, d, J=17.2, 2.2 Hz, 1H, (±)-**33**), 5.04 (br d, J=17.5 Hz, 2H), 5.05 (br d, J=10.0 Hz, 2H), 5.46 (td, J=10.8, 4.4 Hz, 1H), 5.66–5.79 (m, 4H); TLC *meso*-**33** and (±)-**33** R_f=0.66 (hexane/Et_2O, 95:5).

5.30. *S*-[(1*R*,3a*R*,4*R*,7a*R*)-Octahydro-7a-methyl-7-oxo-1-vinyl-1*H*-inden-4-yl] *O*-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] carbonodithioate and *S*-[(1*S*,3a*S*,4*S*,7a*S*)-octahydro-7a-methyl-7-oxo-1-vinyl-1*H*-inden-4-yl] *O*-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] carbonodithioate 34 and *S*-[((3*S*,3a*R*,6*R*,6a*R*)-octahydro-6a-methyl-1-oxo-6-vinylpentalen-3-yl)methyl] *O*-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] carbonodithioate and *S*-[((3*R*,3a*S*,6*S*,6a*S*)-octahydro-6a-methyl-1-oxo-6-vinylpentalen-3-yl)methyl] *O*-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] carbonodithioate 35

Prepared from the mixture of xanthates *meso*-**33** and (±)-**33** (1.0 g, 2.45 mmol) in 1,2-dichloroethane (57 mL) using general procedure. Lauroyl peroxide (0.195 g, 0.49 mmol) was added and the mixture refluxed for 3 h before another 0.2 equiv were added. After 6 h refluxing, the mixture was concentrated in vacuo. The residue was purified by flash chromatography (hexane/Et_2O, 95:5) to give 0.395 g (0.97 mmol, 40%) of an inseparable mixture of diastereomers **34** and 79 mg (0.19 mmol, 8%) of isomer **35** as yellow oils. ^1H NMR **34** (300 MHz, $CDCl_3$) δ 0.81 (d, J=6.9 Hz, 3H), 0.93 (t, J=6.2 Hz, 6H), 1.06 and 1.05 (s, 3H), 1.59–1.95 (m, 14H), 2.20–2.24 (m, 1H), 2.27 ($^1/_2$ AB, dd, J=14.6, 5.7, 1.8 Hz, 1H), 2.59–2.66 (m, 1H), 2.70–2.86 (m, 2H), 4.12 (td, J=11.7, 4.3 Hz, 1H), 5.09 (dt, J=10.8, 1.7 Hz, 1H), 5.10 (dt, J=16.9, 1.6 Hz, 1H), 5.53 (tt, J=10.8, 4.3 Hz,1H), 5.96 (ddd, J=16.9, 10.8, 5.8 Hz, 1H); ^{13}C NMR **34** (75 MHz, $CDCl_3$) δ 12.9, 17.1, 11.2, 20.6, 22.0, 23.9, 24.7, 24.0, 24.8, 26.76, 26.84, 31.4, 34.0, 34.2, 34.3, 38.0, 39.7, 46.5, 47.4, 53.1, 53.5, 57.0, 84.6, 115.6, 138.3, 212.5, 213.4, 213.5; TLC **34** R_f=0.58 (hexane/Et_2O, 95:5); ^1H NMR **35** (300 MHz, $CDCl_3$) δ 0.80 (d, J=6.9 Hz, 3H), 0.92 (t, J=6.7 Hz, 6H), 0.97 (s, 3H), 1.55–2.3 (m, 6H), 2.08–2.30 (m, 4H), 2.53 (br q, J=8.0 Hz, 1H), 2.72 ($^1/_2$ AB, d, J=17.5, 7.0 Hz, 1H), 3.06 ($^1/_2$ AB, d, J=13.5, 8.0 Hz, 1H), 3.42 ($^1/_2$ AB, dd, J=13.5, 5.0, 2.3 Hz, 1H), 4.99 (br d, J=17.3 Hz, 1H), 5.06 (br d, J=10.5 Hz, 1H), 5.52 (tdd, J=10.8, 4.4, 2.3, 1H), 5.76 (ddd, J=17.3, 10.5, 7.1 Hz, 1H); TLC **35** R_f=0.38 (hexane/Et_2O, 95:5).

5.31. *O*-Ethyl *S*-[(1*S*,3a*S*,4*S*,7*R*,7a*S*)-octahydro-7-hydroxy-7a-methyl-7-((*S*)-*N*-methyl-*S*-phenylsulfonimidoyl-*S*-methyl)-1-vinyl-1*H*-inden-4-yl] carbonodithioate 36 and *O*-ethyl *S*-[(1*R*,3a*R*,4*R*,7*S*,7a*R*)-octahydro-7-hydroxy-7a-methyl-7-((*S*)-*N*-methyl-*S*-phenylsulfonimidoyl-*S*-methyl)-1-vinyl-1*H*-inden-4-yl] carbonodithioate 37

To a solution of (*S*)-(+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (0.653 g, 3.90 mmol), prepared from methyl phenyl sulfoxide[49] according to the procedure of Jonhson and co-workers[48] in THF (10 mL) at −10 °C was added *n*-BuLi 1.6 M in hexane (2.3 mL, 3.70 mmol) dropwise and the mixture was stirred during 15 min. At −90 °C, a solution of racemic ketone **16** (1.0 g, 3.36 mmol) in THF (3.5 mL) was added dropwise over 10 min. After 1 h 15 min, the reaction was quenched with a satd NH_4Cl solution and extracted with Et_2O (×3). The combined organic extracts were washed with brine and dried over $MgSO_4$. After filtration and concentration in vacuo, the crude material was purified by flash chromatography eluting with hexane/CH_2Cl_2/EtOAc, 60:37:3 to afford the alcohol as a 1:1 mixture of diastereomers **36**/**37** as white solids (0.357 g+0.445 g, 23%+28%) and 17% of starting ketone **16** as a yellow oil (0.172 g). ^1H NMR **36** (less polar diastereomer, crystals after recrystallization in hot hexane). ^1H NMR **36** (300 MHz, $CDCl_3$) δ 0.81 (s, 3H), 1.41 (t, J=7.2 Hz, 3H), 1.70–2.16 (m, 8H), 2.35 (td, J=12.5, 7.5 Hz, 1H), 2.54 (s, 3H), 2.83 ($^1/_2$ AB, J=13.8 Hz, 1H), 3.09 (q, J=9.5 Hz, 1H), 3.75 (td, J=12.3, 4.0 Hz, 1H), 3.98 ($^1/_2$ AB, J=13.8 Hz, 1H), 4.63 (q, J=7.2 Hz, 2H), 4.82 (br d, J=10.0 Hz, 1H), 5.13 (br d, J=17.0 Hz, 1H), 5.64 (dt, J=17.0, 10.0 Hz, 1H), 7.0 (br s, 1H), 7.77–7.81 (m, 2H), 7.54–7.62 (m, 3H); ^{13}C NMR **36** (75 MHz, $CDCl_3$) δ 10.7, 13.9, 24.7, 27.8, 29.0, 29.3, 33.9, 45.2, 47.2, 49.2, 52.0, 60.2, 69.7, 75.7, 116.2, 128.8 (2C), 129.6 (2C), 133.2, 139.1, 142.0, 215.0; TLC **36** R_f=0.54 (hexane/CH_2Cl_2/EtOAc, 60:37:3); mp=52–54 °C. ^1H NMR **37** (more polar diastereomer) (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.41 (t, J=7.1 Hz, 3H), 1.48–1.63 (m, 5H), 1.71–1.81 (m, 1H), 1.97 (td, J=14.4, 3.8 Hz, 1H), 2.19 (q, J=8.0 Hz, 1H), 2.26–2.35 (m, 1H), 2.57 (s, 3H), 2.81 (dt, J=14.2, 3.3 Hz, 1H), 3.35 ($^1/_2$ AB, J=13.5 Hz, 1H), 3.42 (br, $^1/_2$ AB, J=13.7 Hz, 1H), 3.76 (td, J=12.1, 4.2 Hz, 1H), 4.63 (q, J=7.1 Hz, 2H), 4.87 (dt, J=17.2, 1.4 Hz, 1H), 5.02 (dt, J=10.5, 1.1 Hz, 1H), 6.14 (ddd, J=17.2, 10.5, 6.5 Hz, 1H), 6.80 (br s, 1H), 7.56–7.64 (m, 3H), 7.85–7.88 (m, 2H); ^{13}C NMR **37** (75 MHz, $CDCl_3$) δ 8.9, 13.9, 24.7, 25.2, 28.9, 31.8, 33.8, 48.3, 48.8, 49.0, 52.5, 58.3, 69.8, 76.5, 114.5, 129.1 (2C), 129.8 (2C), 133.4, 139.1, 139.2, 214.1; TLC **37** R_f=0.43 (hexane/CH_2Cl_2/EtOAc, 60:37:3); mp=58–60 °C.

Table 2
Crystal data and structure refinement for **7**, **9**, **23**, and **36**

Compound	**7**	**9**	**23**	**36**
Formula	$C_{24}H_{36}O_4$	$C_{28}H_{31}IN_4O_{12.5}$	$C_{23.5}H_{28}NO_{4.5}S_2$	$C_{23}H_{33}NO_3S_3$
M_w	388.53	750.47	454.61	467.68
Crystal colour	Colorless	Colorless	Colorless	Colorless
Crystal size/mm^3	0.5×0.4×0.25	0.25×0.25×0.15	0.4×0.4×0.15	0.6×0.3×0.3
Crystal system	Orthorhombic	Triclinic	Triclinic	Orthorhombic
Space group	$P2_12_12_1$	$P-1$	$P-1$	$P2_12_12_1$
a/Å	6.477(1)	12.3862(2)	9.0679(5)	7.2265(1)
b/Å	12.640(3)	12.7724(2)	11.6008(7)	12.2799(2)
c/Å	26.067(5)	13.4506(2)	11.9303(7)	27.8022(6)
α/°		92.2411(9)	100.859(3)	
β/°		117.136(1)	106.303(3)	
γ/°		117.6769(7)	105.172(3)	
V/Å^3	2134.09(7)	1589.71(4)	1115.14(11)	2467.19(7)
Z	4	2	2	4
D_c/g cm^{-3}	1.209	1.568	1.354	1.259
μ(Mo Kα)/cm^{-1}	0.8	10.8	2.69	3.24
No. of unique data	2941	7528	3910	3449
No. param. refined	252	406	277	257
$R[I>2\sigma(I)]$	0.058 [2623]	0.055 [6048]	0.056 [3456]	0.049 [2507]
wR [unique]	0.1787	0.158	0.155	0.152
Goodness of fit	1.046	1.04	1.04	1.046
Min; max $\Delta\rho$/e Å^{-3}	−0.351; 0.347	−0.842; 0.688	−0.255; 0.633	−0.299; 0.251

$w=1/[\sigma^2(Fo^2)+(AP)^2+BP]$ where $P=(Fo^2+2Fc^2)/3$.
A=0.0781[a]; 0.1143[b]; 0.0785[c]; 0.0831[d].
B=1.5544[a]; 0.5211[b]; 0.7545[c]; 0.6724[d].

5.32. *O*-Ethyl *S*-[(1*S*,3a*S*,4*S*,7a*S*)-octahydro-7a-methyl-7-oxo-1-vinyl-1*H*-inden-4-yl] carbonodithioate (−)-16 and *O*-ethyl *S*-[(1*R*,3a*R*,4*R*,7a*R*)-octahydro-7a-methyl-7-oxo-1-vinyl-1*H*-inden-4-yl] carbonodithioate (+)-16

A solution of **36** (0.357 g, 0.76 mmol) was heated at 120 °C in xylene (7.6 mL). After 30 h the mixture was concentrated in vacuo. After purification by flash chromatography, (−)-**16** was isolated as a yellow oil with 72% yield (0.163 g, 0.55 mmol). Physical and spectral data were in accordance with the data previously described. ee=99.6% determined by chiral HPLC. $[\alpha]_D^{20}$ −62.98 (*c* 0.524, CH_2Cl_2) for ee=99.6%. (+)-**16** was prepared according to the same procedure, starting with diastereomer **37** (0.445 g, 0.95 mmol). After purification by flash chromatography, (+)-**16** was isolated as a yellow oil with 71% yield (0.202 g, 0.68 mmol). Physical and spectral data were in accordance wih the data previously described. ee=98.3% determined by chiral HPLC. $[\alpha]_D^{20}$ +61.81 (*c* 0.542, in CH_2Cl_2) for ee=98.3%.

5.33. X-ray crystallography

CCDC-272822 (for **7**), CCDC-272821 (for **9**), CCDC-724372 (for **23**), CCDC-724373 (for **36**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk]. A summary of the crystal data, data collection, and refinements is given in Table 2.

Acknowledgements

We are grateful to the *Centre National de la Recherche Scientifique (CNRS)* and the *Ministère de l'Education Nationale* for the financial support. R.R. thanks the *Ministère de l'Education Nationale* for a MENRT fellowship. A.-S.C. is grateful to the 'Région Provence-Alpes-Côte d'Azur' and the *C.N.R.S.* for a grant. We thank Dr. M. Giorgi for X-ray crystal structure determination and Dr. A. Archelas and Dr. A.-L. Bottalla for the chiral GC analysis. We are indebted to Prof. M. Bertrand, Dr. S. Gastaldi (UMR 6517) and Dr. B. Vacher (Pierre Fabre Medicaments) for helpful comments.

References and notes

1. (a) *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic: New York, NY, 1997; (b) *Vitamin D Endocrine System: Structural, Biological, Genetic and Clinical Aspects*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; University of California Riverside: Riverside, CA, 2000.
2. Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200–257.
3. For reviews on this topic, see: (a) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383–1398; (b) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877–1952; (c) Posner, G. H.; Kahraman, M. *Eur. J. Org. Chem.* **2003**, 3889–3895; (d) Chapelon, A. S.; Moraleda, D.; Rodriguez, R.; Ollivier, C.; Santelli, M. *Tetrahedron* **2007**, *63*, 11511–11616.
4. (a) Kabat, M. M.; Radinov, R. *Curr. Opin. Drug Discov. Dev.* **2001**, *4*, 808–833; (b) Okamura, W. H.; Zhu, G.-D.; Hill, D. K.; Thomas, R. J.; Ringe, K.; Borchardt, D. B.; Norman, A. W.; Mueller, L. J. *J. Org. Chem.* **2002**, *67*, 1637–1650 and reference therein.
5. For a review, see: Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071–12150.
6. Steroidal numbering is used.
7. (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskoković, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945–2948; (b) Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 5311–5320; (d) Daniewski, A. R.; Kiegiel, J. *J. Org. Chem.* **1988**, *53*, 5534–5535; (e) Fernàndez, B.; Martinez Pérez, J. A.; Granja, J. R.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1992**, *57*, 3173–3178; (f) Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071–12150; (g) Daniewski, A. R.; Liu, W. *J. Org. Chem.* **2001**, *66*, 626–628; (h) Chochrek, P.; Wicha, J. *Org. Lett.* **2006**, *8*, 2551–2553; (i) Chochrek, P.; Kurek-Tyrlik, A.; Michalak, K.; Wicha, J. *Tetrahedron Lett.* **2006**, *47*, 6017–6020.
8. (a) Pardo, R.; Archier, P.; Santelli, M. *Bull. Soc. Chim. Fr.* **1986**, 760–765; (b) Gordon, H. L.; Freeman, S.; Hudlicky, T. *Synlett* **2005**, 2911–2914 and references therein.
9. Allinger, N. L.; Tribble, M. T. *Tetrahedron* **1972**, *28*, 1191–1202.
10. Lo Cicero, B.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, *46*, 914–919.
11. (a) Quinkert, G. *Experientia* **1957**, *13*, 381–389; (b) Inhoffen, H. H.; Quinkert, G.; Schutz, S.; Kampe, D.; Domagk, G. F. *Chem. Ber.* **1957**, *90*, 664–673.
12. Pellissier, H.; Toupet, L.; Santelli, M. *J. Org. Chem.* **1994**, *59*, 1709–1713.
13. Mariet, N.; Pellissier, H.; Ibrahim-Ouali, M.; Santelli, M. *Eur. J. Org. Chem.* **2004**, 2679–2691.
14. (a) Rodriguez, R.; Ollivier, C.; Santelli, M. *Tetrahedron Lett.* **2004**, *44*, 2289–2292; *trans*-Hydrindanone precursors of CD-ring system of vitamin D have previously been obtained from *meso*-**3**, for premilary communications see: (b) Rodriguez, R.; Ollivier, C.; Santelli, M. *Synlett* **2006**, 312–314; (c) Chapelon, A.-S.; Ollivier, C.; Santelli, M. *Tetrahedron Lett.* **2006**, *47*, 2747–2750.
15. For reviews, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370; (b) Hartung, J.; Greb, M. *J. Organomet. Chem.* **2002**, *661*, 67–84.
16. (a) Mitome, H.; Miyaoka, H.; Yamada, Y. *Tetrahedron Lett.* **2000**, *41*, 8107–8110; (b) Gonzalès-Avión and Mouriño showed that different substituents at the C_{12} position increased to 4.4 times the affinity of the related calcitriol analogs for

the vitamin D receptor (VDR). Gonzalès-Avión, X. C.; Mouriño, A. *Org. Lett.* **2003**, *5*, 2291–2293.
17. First, we considered a ketone-directed epoxidation of *anti meso*-**3**. Attempts performed with *meta*-chloroperbenzoic acid at rt led to a 50:50 mixture of two monoepoxides diastereoisomers, resulting from a total lack of facial selectivity.
18. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
19. (a) Sabitha, G.; Satheesh Babu, R.; Rajkumar, M.; Srinivas Reddy, Ch.; Yadav, J. S. *Tetrahedron Lett.* **2001**, *42*, 3955–3958; (b) Bartoli, G.; Marcantoni, E.; Sambri, L. *Synlett* **2003**, 2101–2116.
20. For the preparation of a ^{13}C-labeled CD-ring by S_N2 cycloalkylation of the corresponding seco-iodo compound, see: Okamura, W. H.; Zhu, G.-D.; Hill, D. K.; Thomas, R. J.; Ringe, K.; Borchardt, D. B.; Norman, A. W.; Mueller, L. J. *J. Org. Chem.* **2002**, *67*, 1637–1650.
21. For a review, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
22. Separation of both diastereoisomers at the previous stage should provided a better er. Unfortunatly, attemps to remove the minor stereoisomer by flash chromatography were unfruitful. Efforts to solve this problem are still under studies.
23. The enatiomeric ratio (er) was calculated from the chiral GC values of (+)-**4**, **8a** and **8** as detailed in experimental section.
24. (a) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1290–1293; (b) Blakemore, P. R.; Grzywacz, P.; Kocienski, P. J.; Marczak, S.; Wicha, J. *Pol. J. Chem.* **1999**, *73*, 1209–1217; (c) Blakemore, P. R.; Kocienski, P. J.; Marczak, S.; Wicha, J. *Synthesis* **1999**, 1209–1215.
25. (a) Plesniak, K.; Zarecki, A.; Wicha, J. *Top. Curr. Chem.* **2007**, *275*, 163–250; (b) Kocienski, P. J. *Chem. Ind.* **1981**, 548–551; (c) Kocienski, P. J. *Phosphorus Sulfur Silicon Relat. Elem.* **1985**, *24*, 477–507; (d) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28; (e) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365–366.
26. Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836.
27. For reviews on the chemistry of xanthates, see: (a) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002–6016; (b) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201–236; Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672–685; (c) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *153–154*, 137–145; (d) Zard, S. Z. In *Radical in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M., Eds.; Wiley-VCH GmbH: Weinheim, Germany, 2001; p 90.
28. For examples of cyclization of an α-carbonyl radical generated from the corresponding xanthate, see: (a) Bacqué, E.; Pautrat, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 325–328; (b) Briggs, M. E.; El Qacemi, M.; Kalaï, C.; Zard, S. Z. *Tetrahedron Lett.* **2004**, *45*, 6017–6020.
29. Pellissier, H.; Santelli, M. *Tetrahedron* **1996**, *52*, 9093–9100.
30. Ester and malonate xanthate derivatives have been reported to be synthetized by reaction of their respective enolates with diethyl bisdithiocarbonate in 50–58% yield. (a) Maslak, V.; Čeković, Ž; Saičić, R. N. *Synlett* **1998**, 1435–1437; (b) Shi, L.; Chapman, T. M.; Beckman, E. J. *Macromolecules* **2003**, *36*, 2563–2567.
31. Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386–392.
32. For a review on acyl radicals see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991–2070.
33. (a) Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1520–1523; (b) Porter, N. A.; Chang, V. H.-T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554–3560; (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140–3157.
34. Broeker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651–3655.
35. UB3LYP/6-31G* calculations provide the values of reaction barriers, reaction enthalpies and partial bond lengths in the transition state for the cyclization of radicals comparable of those computed using perturbation theory UMP2/6-31G*, see: Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. *J. Am. Chem. Soc* **2002**, *124*, 10765–10772.
36. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision D.02*; Gaussian: Pittsburgh, PA, 2003.
37. (a) Bruice, T. C.; Lightstone, F. C. *J. Am. Chem. Soc.* **1996**, *118*, 2595–2605; (b) Repasky, M. P.; Guimarães, C. R. W.; Chandrasekhar, J.; Tirado-Rives, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2003**, *125*, 6663–6672; (c) Pintér, B.; De Proft, F.; Van Speybroeck, V.; Hemelsoet, K.; Waroquier, M.; Chamorro, E.; Veszprémi, T.; Geerlings, P. *J. Org. Chem.* **2007**, *72*, 348–356.
38. Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128–134.
39. Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153–161.
40. Bauschlicher, C. W., Jr.; Partridge, H. *J. Chem. Phys.* **1995**, *103*, 1788–1791.
41. (a) Mori, K.; Nakamura, Y. *J. Org. Chem.* **1969**, *34*, 4170–4172; (b) Boivin, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 6877–6880; (c) Boivin, J.; Pothier, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 9239–9241.
42. Chen, C. H. *J. Heterocycl. Chem.* **1976**, *13*, 1079–1084.
43. Martel, S.; Prandi, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 305–315.
44. Cane, D. E.; Yang, G.; Coates, R. M.; Pyun, H. J.; Hohn, T. M. *J. Org. Chem.* **1992**, *57*, 3454–3462.
45. Srikrishna, A.; Kumar, P. P. *Tetrahedron* **2000**, *56*, 8189–8195.
46. (a) He, A.; Yan, B.; Thanavaro, A.; Spilling, C. D.; Rath, N. P. *J. Org. Chem.* **2004**, *69*, 8643–8651; (b) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yaun, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964–2969; (c) Calvet, G.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2007**, *9*, 1485–1488; (d) Matsui, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1853–1865.
47. (a) Carrea, A.; Denis, J. N.; Greene, A. E. *Synth. Commun.* **1991**, *21*, 1–9; (b) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Grassi, G.; Piperno, A.; Privitera, T.; Romeo, G. *Tetrahedron* **2001**, *57*, 3425–3433.
48. (a) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021–4023; (b) Johnson, C. R.; Zeller, J. R. *Tetrahedron* **1984**, *40*, 1225–1233; (c) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909–912; (d) Shiner, C. S.; Berks, A. J. *J. Org. Chem.* **1988**, *53*, 5542–5545; (e) Kraehenbuehl, K.; Picasso, S.; Vogel, P. *Helv. Chim. Acta* **1998**, *81*, 1439–1479.
49. Weber, J. V.; Schneider, M.; Salami, B.; Paquer, D. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 99–102.
50. (a) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594–6598; (b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418–7423.
51. Boga, C.; Del Vecchio, E.; Forlani, L.; Todesco, P. E. *J. Organomet. Chem.* **2000**, *601*, 233–236.