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Enantioselective Synthesis of The Hexahydronaphthalene Nucleus of (-)-Compactin from Ethyl (1R,2S)-2-Methyl-4-oxocyclohexanecarboxylate and 2-(3-Nitropropyl)-1,3-dioxolane as Four Carbon Bifunctional Annelating Agent.#

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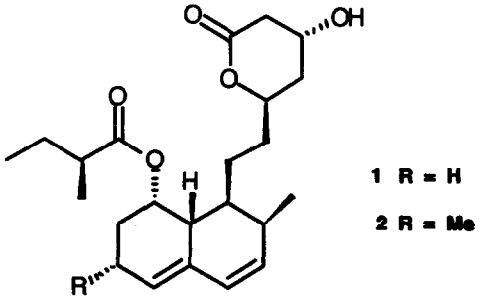
Abstract: An enantioselective approach to the synthesis of the hexahydronaphthalene nucleus of natural compactin is described. The key elements of the synthesis are as follows: (i) the preparation of the chiral starting material through enzymatic resolution of the readily available *cis* 2-methyl-4-oxocyclohexane carboxylic acid, (ii) conversion into the suitably protected (4S,5S)-4-hydroxymethyl-5-methyl-2-cyclohexen-2-one by regioselective introduction of the α,β-carbon-carbon double bond by Pd(II)-catalyzed dehydrosilylation, (iii) construction of the new six-membered ring into the preexisting carbon skeleton using 2-(3-nitropropyl)-1,3-dioxolane as a four carbon bifunctional annelating reagent, (iv) elaboration of the derived hexahydronaphthalenone to an advanced precursor already taken to the natural target by functional group manipulation, including conversion of the nitro group to the oxygenated function at C-1 and dehydration of an allylic alcohol precursor to the required 1,3-diene moiety.

Compactin **1**, also known as ML 236B, first isolated[1] in 1976 from *Penicillum brevicompactum*, and mevinolin **2** are the best-known members of a series of fungal metabolites called mevinic acids, which have attracted a great deal of interest owing to their ability to inhibit HMG-CoA reductase, a rate-limiting enzyme in cholesterol biosynthesis.

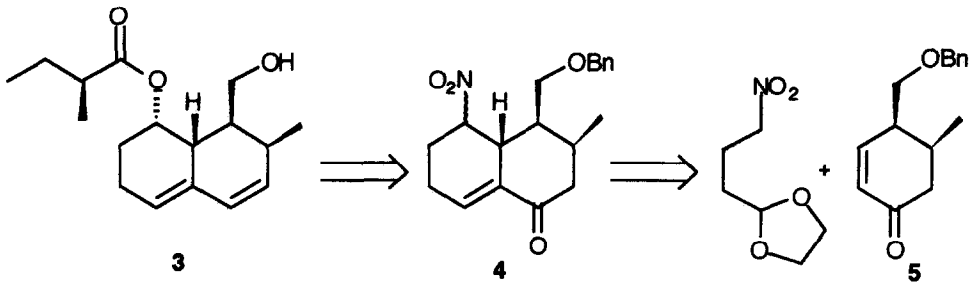


1 R = H

2 R = Me

Not surprisingly, the challenge of providing new synthetic routes to the mevinic acids has stimulated many approaches and successes.[2] After considering various possible retrosynthetic analyses, we decided to use the methodology outlined in Scheme I to prepare the decalin fragment containing four contiguous asymmetric centers.

SCHEME I



Thus, the hexahydronaphthalene nucleus of the known[2b] precursor **3** with its full complement of stereogenic centers was envisaged to arise from the intermediate **4** containing strategically situated functions for the elaboration of the conjugated diene and a functional group at the C-1 position that could be manipulated to the required oxygenated function. The ring A could in turn be built onto a preformed ring B portion **5**, readily obtained in optically active form, using 2-(3-nitropropyl)-1,3-dioxolane as four carbon bifunctional annelating agent. An additional positive aspect is that this strategy places an hydroxymethyl group at C-8, which could serve as a handle for the construction of the δ-lactone fragment. Moreover, it would readily allow the incorporation of different groups at the C-3 position. With respect to other approaches relying on the use of the starting 4,5-disubstituted-cyclohex-2-enone as preformed ring B, our approach differs both in the preparation of this material, previously utilized as racemic compound, in optically active form and in the means by which ring A is built onto the ring B portion.

The starting material:

The reputation of racemic *cis* 2-methyl-4-oxo-cyclohexane carboxylic acid **7**, prepared by hydrolysis of the corresponding ester **6**, easily obtained by catalytic reduction of the commercially available Hagemann's ester, for being difficult to resolve by classical methods caused us some initial trepidation. Commercial facilities allowed Crenshaw et al.[3] to overcome this hurdle, providing them 10g of (+)-**7** and 15.6g of (-)-**7** starting from 260g of (±)-**7**, as reported without details in a footnote of their paper dealing with the synthesis of steroid analogues. In addition, while the optical purity of the two enantiomers has been determined by ^{1}H NMR analysis of diastereoisomeric esters formed with methyl (-)-mandelate, the absolute configuration has been only tentatively assigned on the basis of the biological activities of some derivatives.

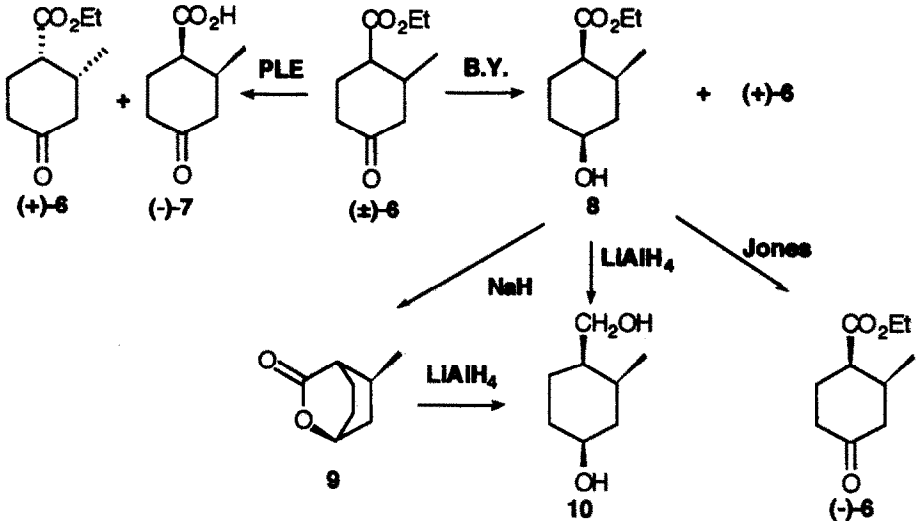
However, we found that chemo-enzymatic approaches served to achieve this task conveniently. The first approach is centered on the well known ability of Baker's yeast to perform asymmetric reduction of ketones.[4]

While much work continues to be done on the reduction of both acyclic and cyclic β–keto esters, largely because of the usefulness of the available models for predicting the absolute stereochemistry of the products, less attention has been reserved to the corresponding γ and δ-keto esters. Therefore, we submitted the δ-keto esters (±)-**6** to typical fermenting conditions, hoping that enantioselective reduction and concomitant kinetic

resolution might lead to good enantiomeric purity of the products. Unfortunately, at least under the experimental conditions adopted, Baker's yeast showed a good diastereoselectivity, providing almost exclusively the *cis*- hydroxyester (-)-**8**, but only very modest ability to resolve kinetically racemic (±)-**6**, the recovered (+)-**6** showing a low enantiomeric excess.

We have also observed a lowering of optical purity of the hydroxyester (-)-**8** by prolonging the reaction time of Baker's yeast reduction of (±)-**6** from 15 hours to 70h, with concomitant recovering of the keto ester (+)-**6** with $[\alpha]_D^{20}$ = +9.1 and e.e. = 76%, according with the observed moderate kinetic resolution power of Baker's yeast on this substrate. Jones oxidation of (-)-**8** gave (-)-**6**, the enantiomeric purity of which has been determined by ^{1}H NMR analysis of diastereoisomeric ketals formed with (2R,3R)-butanediol. Moreover, the formation of the lactone (+)-**9** by treatment of the hydroxy ester (-)-**8** with NaH in THF served to establish the geometric relationship between the substituents on the cyclohexane ring. Both (-)-**8** and (+)-**9** were easily converted to the diol (-)-**10** by treatment with $LiAlH_4$.* All these transformations are summarized in Scheme II.

SCHEME II



A second and more convenient approach to the resolution of (±)-**6** was based on the employment of pig liver esterase, one of the most useful enzymes for the preparation of chiral synthons, routinely utilized for carrying out enantioselective hydrolyses of ester-containing substrates.[5] Moreover, the simple and easy to use active-site model recently developed by Jones et al.[6] for the prediction of both the stereochemical sense of pig liver esterase-catalyzed hydrolyses, as well as the level of enantiomeric excess which can be expected for new substrates, has significantly enhanced the potential of pig liver esterase, especially when new synthetic applications are being exploited.

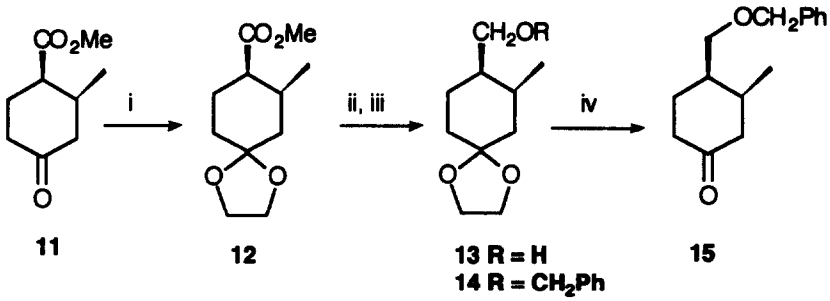
We thought of interest to verify the predictive value of the active-site model when applied to (±)-**6** not only to resolve the racemic mixture but also to confirm the stereochemical results obtained by using Baker's yeast. On the other hand, this substrate is structurally very close to *cis* (±)-1-carbomethoxy-2-methyl-cyclohexane,

belonging to a series of racemic monocyclic esters utilized by Jones[6] for predicting and interpreting the stereochemical outcome of the pig liver esterase-catalyzed hydrolyses.

Thus, submitting (±)-**6** to pig liver esterase, following the recommended general procedure, namely permitting hydrolysis to continue until one half equivalent of base had been consumed, we recovered in excellent yield the ester (+)-**6** with $[\alpha]_D^{20}$ = +10.0 (e.e.= 91%) through extraction of the reaction mixture at neutral pH. The corresponding carboxylic acid (-)-**7** isolated after acidification, followed by extraction showed $[\alpha]_D^{22}$ = -14.51. The e.e. of the ester (+)-**6** was determined by gas-chromatography using chiral stationary phase, while the o.p. of the carboxylic acid derivative (-)-**7** was determined by comparison of its optical rotation with that of the enantiomeric pure compound reported in literature.[3a]

Having in hand useful amounts of (+)-**7** with good optical purity, we undertook its chemical conversion into (4S,5S)-4-hydroxymethyl-5-methyl-2-cyclohexen-1-one **5**, which has been recently prepared[7] through a different chemo-enzymatic approach, while the racemic compound has been already utilized as intermediate for the synthesis of mevinic acids.[2b,8] In the Scheme III are summarized the operations involved in the synthetic sequence which began with the esterification of (-)-**7** with ethereal diazomethane to the corresponding ester **11**, followed by ketalization under standard conditions to give **12** and subsequent $LiAlH_4$ reduction of the ester function to produce almost quantitatively the primary alcohol **13**.

SCHEME III



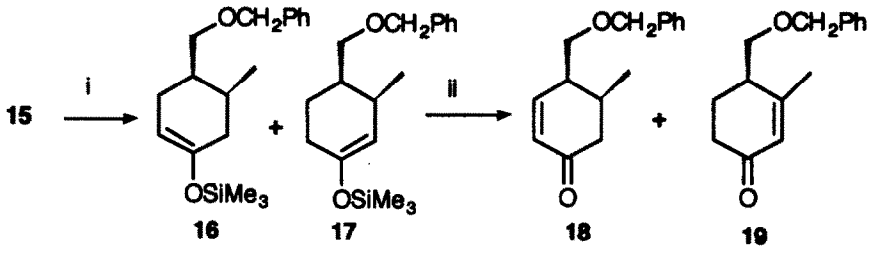
11 **12** **13 R = H** **14 R = CH_2Ph** **15**

Reagents: i, $(CH_2OH)_2$, H^+; ii, $LiAlH_4$; iii, $PhCH_2Br$, NaH, $Bu_4N^+I^-$; iv, H^+, H_2O.

Although several protective groups should be compatible with the proposed chemistry, we conservatively settled for a benzyl ether protecting group, anticipating its final removal in a Lewis acid catalyzed reaction. Thus, treatment of **13** with benzyl bromide and sodium hydride in the presence of tetrabutyl ammonium iodide[9] gave easily the corresponding benzyl ether **14**, which was subsequently transformed into the saturated ketone **15** by removal of the ketal protecting group by aqueous acid treatment.

The introduction of the α,β-carbon-carbon double bond to unsymmetrical ketones such as **15** is often complicated by lack of regioselectivity. However, the experimentally simple $Pd^{II}(OAc)_2$-induced dehydrosilylation[10] of the silyl enol ethers applied to the 9:1 mixture of silyl enol ethers **16** and **17** obtained by trapping with Me_3SiCl the regioisomeric enolates generated by treatment with LDA in THF -78°C of **13**, allowed a regiospecific introduction of the α,β-carbon-carbon double bond, providing conveniently in 75% yield the desired intermediate **18** after column chromatography to remove the unwanted isomer **19**, setting the stage for the subsequent annelation.(Scheme IV)

SCHEME IV



Reagents: i, LDA, Me_3SiCl; ii, $Pd^{II}(OAc)_2$.

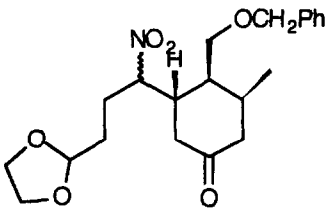
At this point, our synthetic plan called for a methodology for the construction of the new six-membered ring into pre-existing carbon skeleton of **18**, forming the new carbon-carbon bonds to the α and β carbons of the cycloalkenone, as in the classical Diels-Alder reaction. However, within the last decade alternative strategies for annulation based on the utilization of bifunctional reagents has emerged as a highly versatile method.[11-16]

2-(3-Nitropropyl)-1,3-dioxolane as four carbon bifunctional annelating agent.

Although the use of 4-nitrocarbonyl as anellating reagents was described as early as 1976,[17] this strategy has not been used to a significant extent in synthesis despite its apparent potential.[18] Propanal and butanal acetals bearing at β- and γ-position respectively a functional group suitable for C-C bond formation are widely utilized as three- and four-carbon homologating agents, a common operation in organic synthesis. Thus, the acetals of 3- and 4-haloalkanals have been frequently used[16,19] both as alkylating reagents or umpoled through conversion under special conditions to organo-lithium or Grignard reagents, while 2-(2-nitroethyl)-1,3-dioxolane, conveniently prepared by 1,4-nitrite addition to acrolein followed by standard acetalization, has been shown to act as convenient 3-oxopropyl anion synthon.[20,21] Surprisingly, despite a pertinent accumulation of nitroalkane chemistry as versatile building blocks, the homologous 2-(3-nitropropyl)-1,3-dioxolane, has found only limited applications,[22,23] probably because its preparation employing Triton B as catalyst to promote the 1,4-addition product of nitromethane to acrolein proceeds with disappointingly low yield (15%).[24] Improved procedures for the preparation of 4-nitropropanals through Michael addition of nitroalkanes to acrolein in the presence of a variety of catalysts continue to appear in the literature, although, rather curiously, the lower alkane employed is invariably nitroethane. However, the protocol suggested by Miyakoshi,[25] involving the use of tributylphosphine to catalyze the addition of nitromethane to acrolein, followed by in situ acetalization of the resulting adduct under standard conditions (ethylene glycol in the presence of p-toluenesulfonic acid), provides 2-(3-nitropropyl)-1,3-dioxolane in satisfactory overall yield (47%), thus allowing its utilization as convenient 4-oxopropyl anion equivalent both as annelating and homologating agent. The specific reagent that we have chosen to study undergoes smooth 1,4-conjugate addition with both cyclopent-2-en-1-one and cyclohex-2-en-1-one in the presence of potassium tert-butoxide in THF. The resulting isolated adducts were subsequently treated with hydrochloric acid to induce sequential acetal hydrolysis and intramolecular aldol condensation and dehydration, producing the bicyclic annulation products in good yield as mixture of diastereomers, which could be easily separated by column chromatography. Encouraged by these results, we submitted the cyclohexenone **19** to the annulation sequence with 2-(3-nitropropyl)-1,3-dioxolane in the presence of potassium tert-butoxide

in THF. The reaction proceeded uneventfully to give the initial 1,4-addition product **20** in 83%, as a diastereomeric mixture at one of the newly introduced chiral centers, namely at the carbon bearing the nitro group, but with the stereochemistry corresponding to the natural product at the carbon bearing the attached side chain, the two substituents on the cyclohenone ring playing a fundamental directing effect in the formation of the carbon-carbon bond in the Michael addition. The crude mixture was then submitted to the required aqueous acid conditions to promote the sequential transformations leading to the formation of the cyclized product **21**.

The fact that two epimers are obtained does not matter as the stereochemistry at C-1 is easily adjusted at a later stage, after conversion of the nitro group into a carbonyl.



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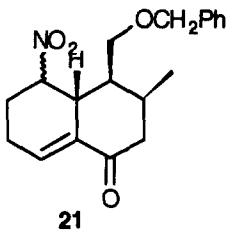

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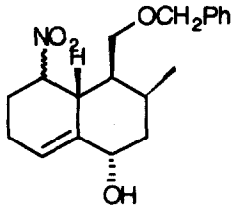

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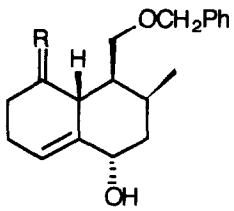
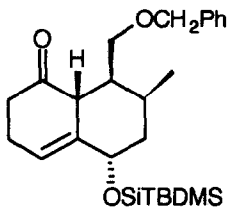


23 R = NOH
24 R = O



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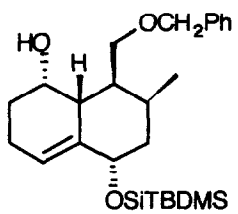

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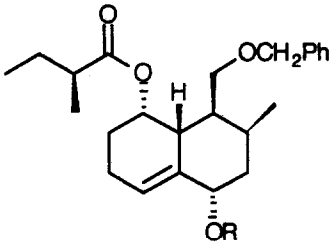
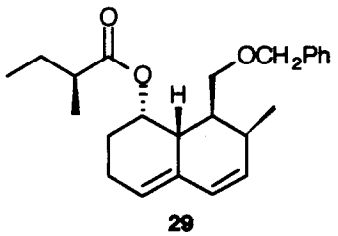
Thus, after reduction of the enone with sodium borohydride and cerium trichloride[26] to the corresponding allylic alcohol **22**, the nitro group was oxidatively processed by treatment with 30% hydrogen peroxide[27] in aqueous methanol in the presence of potassium carbonate to afford the crystalline oxime **23** in 52% isolated yield, subsequently converted quantitatively to the parent ketone **24** by action of aqueous $TiCl_3$. Of the various methods examined, the most reliable procedure to achieve this conversion was clearly this two-step sequence.

As expected, this transformation led to the formation of a single product, the new asymmetric center being stereoselectively generated in the previous reductive step. Instead of completing the required 1,3-diene moiety at this point, we felt that this operation might be best carried out after adjustment of the oxidation level at C-1. Consequently, the allylic hydroxyl function of **24** required protection as the corresponding tert-butyldimethylsilyl ether **25**, which was then stereoselectively transformed to the axial alcohol **26** with lithium aluminum tri-tert-butoxide hydride and easily acylated with (S)-2-methylbutyric acid to afford the crystalline ester **27**. Dehydration of the allylic alcohol **28**, easily derived from **27** by desilylation by mild acid treatment with p-toluensulfonic acid, was the last step required for the completion of the diene moiety. This dehydration was unsuccessfully attempted under a variety of experimental conditions including basic aluminum oxide[2c] or Martin reagent.[2d]

Better results were obtained by treatment of **28** with methansulfonyl chloride in pyridine giving rise to the predominant formation of the desired unrearranged diene **29** isolated in acceptable yield by flash chromatography, although contaminated by a small amount of the rearranged diene **30**.



27 R = TBDMS
28 R = H



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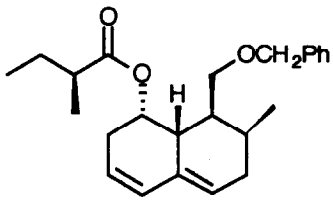

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For the purpose of sample comparison and to intersect with Heathcock's synthesis allowing the completion in formal sense of the total synthesis of compactin, we effected final debenzylation with boron trichloride in dichloromethane at -78°C obtaining the crystalline **3** in 40% yield, which was found to have physical constants (^{1}H NMR, [α] in excellent agreement with those reported.[2b]

Experimental.

General remarks. Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel coated plates F_{254} (Merck). Infrared (IR) spectra were measured on a Perkin-Elmer Model 297. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AC-200 spectrometer for solutions in $CDCl_3$ unless otherwise noted and peak positions are given in parts per millions downfield from tetramethylsilane as an internal standard. Coupling constants are given in Hz. Optical rotations were measured on a Perkin-Elmer polarimeter 241. Organic solutions were dried over anhydrous magnesium sulphate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling range 40-60°C and ether to diethyl ether. Flash-chromatography was carried out with Merck silica gel (230-400 mesh). All reactions were carried out under N_2 atmosphere. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

Ethyl 1R-(1α,2α,4α)-4-hydroxy-2-methyl-cyclohexancarboxylate 8.
Baker's yeast (50g) was added to a suspension of (±)-**6** (7g, 3.8mmol) in distilled water (1300ml) and the mixture rapidly stirred at 30°C open to air for 15h. After filtration, the filtrate was saturated with NaCl and extracted with EtOAc (3x500ml). The dried organic extracts were concentrated and the residue purified by column chromatography (eluent: ether: light petroleum 4/6) to give **8** (1.2g, 17%), $[\alpha]^D_{22}$ = -20 (c, 1.13, $CHCl_3$), as colorless oil and recovered starting material (5g). IR (neat): 3400, 1730 cm^{-1}; ^{1}H NMR: δ 1.03 (d, 3H, J=6.4), 1.26 (t, 3H, J=7), 1.4-1.9 (m, 7H), 1.95-2.1 (m, 1H, 2.5 (m, 1H), 3.6 (m, 1H) 4.12 (q, 2H, J=7). (Found: C, 64.29; H, 9.51. $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74).

5S-(1β,4β,5α)-5-Methyl-3-oxo-2-oxabicyclo[2.2.2.]-octane 9.

A solution of **8** (1g, 5.38mmol) in THF (15ml) was added dropwise to an ice-cooled suspension of 70% sodium hydride (0.187g, 5.55mmol) in THF (20ml). After being stirred for 6h at room temperature the mixture was treated with aqueous NH_4Cl (10ml) and extracted with EtOAc (3x25ml). The dried extracts were concentrated under reduced pressure and the residue purified by flash-chromatography (eluent: ether: light petroleum 7:3) to afford **9** (0.6g, 80%), $[\alpha]^D_{22}$ = +68.1 (c,0.985, $CHCl_3$), as an oil. IR (neat): 1750 cm^{-1}; ^1H NMR: δ 1.05 (s, 3H, J=6.7), 1.4-2.2 (m, 7H), 2.5 (m, 1H), 4.68 (s, 1H). (Found: C, 68.39; H, 8.51. $C_8H_{12}O_2$ requires C, 68.55; H, 8.63).

1S-(1α,3α,4α)-4-Hydroxymethyl-3-methyl-cyclohexan-1-ol 10.

a) From **8**: a solution of **8** (0.28g, 2mmol) in THF (5ml) was added dropwise to an ice-cooled suspension of $LiAlH_4$ (0.38g, 10mmol) in THF (20ml). After being stirred for 3h, the mixture was treated with 5% HCl (10ml) and extracted with EtOAc (3x25ml). The dried organic extracts were evaporated to leave **10** (0.22g, 80.8%), $[\alpha]^D_{22}$ = -27.0 (c,1.13, $CHCl_3$), as a pale green oil. IR (neat): 3330 cm^{-1}; ^1H NMR: δ 0.99 (d, 3H, J=6.7), 1.1-1.4 (m, 3H), 1.7-1.9 (m, 7H), 3.6-3.7 (m, 3H). (Found: C, 66.49; H, 10.51. $C_8H_{16}O_2$ requires C, 66.63; H, 11.18).

b) From **9**: the reduction of **9** (0.25g, 1.34mmol) with $LiAlH_4$ (0.10g,2.6mmol) in THF (20ml) gave rise after usual work-up to **10** (0.17g, 85%), $[\alpha]^D_{22}$ = -26.2 (c, 0.85, $CHCl_3$), as an oil. IR (neat): 3330 cm^{-1}; ^1H NMR: δ 0.98 (d, 3H, J=6.8), 1.1-1.4 (m, (4H), 1.7-1.76 (m, 4H), 1.93-2.05 (m, 1H), 2.14 (s, 1H), 3.54-3.7 (m, 3H).

Ethyl 1R-(1α,2α)-(-)-2-Methyl-4-oxo-cyclohexancarboxylate 6.

To an ice-cooled solution of (0.15g, 0.82mmol) in acetone (15ml) was added Jones reagent dropwise until a reddish color persisted. After excess oxidant was quenched with EtOH, anhydrous $MgSO_4$ was added and the green mixture was filtered through Celite. Removal of the solvent under reduced pressure and flash chromatography of the residue (eluent: ether : light petroleum 2:3) afforded **(-)-6** (0.11g, 72.5%) as colorless oil, $[\alpha]^D_{22}$ = -11.0 (c, 0.55, $CHCl_3$): IR (neat): 1730 cm^{-1}; ^1H NMR: δ 0.97 (d, 3H, J=6.9), 1.29 (t, 3H, J=7.18), 2.3-2.55 (m, 7H), 2.83-287 (m,1H), 4.18 (q, 2H, J=6.7). (Found: C, 65.09; H, 8.51) $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75).

Methyl 1R-(1α,2α)-(-)-2-Methyl-4-oxo-cyclohexancarboxylate 11.

PLE (1500units) was added to a stirred solution of **(±)-6** (2.9g, 4.35mmol) in distilled water (33ml) at room temperature while the pH was maintained at 7.0 by addition of 0.2M NaOH with a pH stat. The hydrolysis was permitted to continue until one-half equivalent of base had been consumed. The reaction mixture was immediately extracted with EtOAc (3x20ml), the dried organic extracts were concentrated under reduced pressure to give the residual ester **(+)-6** (1.1 g, 45%) $[\alpha]^D_{22}$ = +11.35. The aqueous phase was acidified to pH 2.0 with 6M HCl and reextracted with EtOAc (3x25ml). Evaporation of the organic extracts gave the solid acid **7** which, after crystallization from ether : pentane 3:1, m.p.85-86°C, $[\alpha]^D_{22}$ = -12.0 (c, 0.55, $CHCl_3$), was directly submitted to ethereal diazomethane to produce quantitatively the methyl ester **11** as an oil, $[\alpha]^D_{22}$ = -14.51 (c, 3.66, $CHCl_3$), IR: 1730 cm^{-1}; ^1H NMR: δ 0.95-0.98 (d, 3H, J=6.7), 2.01-2.61 (m, 7H), 2.83-2.92 (m, 1H), 3.72 (s, 3H). (Found: C, 63.39; H, 8.11. $C_9H_{14}O_3$ requires C, 63.51; H, 8.29).

Methyl 1R-(1α,2α)-2-Methyl-4-ethylenedioxycyclohexancarboxylate 12.

A solution of **11** (8.5 g, 50mmol) in toluene (50ml) containing p-toluenesulfonic acid (0.2mg) was heated at reflux for 2h with a Dean-Stark trap. The cooled solution was washed with aqueous $NaHCO_3$ (25ml), dried and evaporated in vacuum. Distillation of the crude product afforded **12** (10g, 93%) as an oil, $[\alpha]^D_{22}$ = -3.0 (c, 1.17, $CHCl_3$), IR: 1730 cm^{-1}; ^1H NMR: δ 0.97–1.0 (d, 3H, J= 6.99), 1.49-2.20 (m, 7H), 2.53-2.61 (m, 1H), 3.66 (s, 3H), 3.90-3.98 (m, 4H). (Found: C, 62.79; H, 6.51. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.71).(Found: C, 62.19; H, 8.51).

7R-(7α,8α)-(-)-7-Hydroxymethyl-8-methyl-1,4-dioxaspiro[4,5]decane 13.

A solution of **12** (11.4, 0.53mmol) in dry ether (40ml) was added to an ice-cooled slurry of $LiAlH_4$ (1.8g, 47mmol) in dry ether (50ml) and the mixture left at room temperature for 3h. Careful addition of water (3ml) allowed the separation of the organic layer from inorganic salts, which were washed with EtOAc (5x25ml) by decantation. The combined organic extracts were dried and evaporated in vacuo to yield **13** (9.1 g, 92%) as an oil, bp 85-87°C at 0.01mmHg, $[\alpha]^D_{22}$ = -15.3 (c, 1.11, $CHCl_3$): IR (neat): 3350 cm^{-1}; ^1H NMR: δ 0.95 (d, 3H, J=7.3), 1.4-1.8 (m, 8H), 2.05 (s, 1H), 3.5-3.7 (m, 2H), 3.9-3.97 (m, 4H). (Found: C, 64.39; H, 9.51., $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74).

[7R-(7α,8α)]-(-)-7-Benzyloxymethyl-8-methyl-1,4-dioxaspiro[4,5]decane 14.
A solution of **13** (14.6, 78.5mmol) in THF (50ml) was added dropwise to an ice-cooled suspension of 70% sodium hydride (2.72g, 79.62mmol) in THF (20ml). After being stirred for 10min, benzyl bromide (9.42ml, 79.03mmol) and tetrabutyl ammonium iodide (0.28g, 0.78mmol) were added and the mixture stirred at room temperature for 24h. After removal of most of the solvent in vacuo, the residue was treated with EtOAc and water (40ml each). The organic layer was separated, dried and concentrated to yield **14** (19.5 g, 90%) as an oil, bp 110-120°C at 0.01mmHg, $[\alpha]^{D}_{22}$ = -15.3 (c, 1.02, $CHCl_3$): IR (neat): 1450, 1360 cm^{-1}; ^1H NMR: δ 0.95-0.91 (d, 3H, J=7.2), 1.4-2.1.8 (m, 8H), 3.36-3.52 (m, 2H), 3.88 (m, 4H), 4.45-4.53 (d, 2H, J=3.1), 7.31-7.37 (m, 5H). (Found: C, 73.69; H, 8.57. $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75).

[3R-(3α,4α)]-(-)-4-Benzyloxymethyl-3-methylcyclohexanone 15.
To a solution of **14** (4.7g, 17mmol) in THF (30ml) 5% HCl (6ml) was added and the mixture stirred for 12h at room temperature. After removal of most of the solvent in vacuo, the residue was treated with EtOAc and water (40ml each). The organic layer was separated, dried and concentrated to yield **15** (3.17 g, 80%) as an oil, bp 102-104°C at 0.01mmHg, $[\alpha]^{D}_{22}$ = -10.7 (c, 1.31, $CHCl_3$): IR (neat): 1720, 1500 cm^{-1}; ^1H NMR: δ 0.82-0.86 (d, 3H, J=7.4), 1.58-2.55 (m, 8H), 3.41-3.45 (d, 2H, J=7), 4.53 (s, 2H), 7.32-7.36 (m, 5H).(Found: C, 77.41; H, 8.57. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68).

[4S-(4α,5α)]-(-)-4-Benzyloxymethyl-5-methyl-2-cyclohexen-1-one 18.
A solution of **15** (2g, 8.62mmol) in THF(10ml) was added dropwise at -78°C to a solution of LDA [from 1.6M BuLi (6ml, 9.13mmol) and diisopropyl amine (1.46ml, 10.3mmol) in THF (20ml)]. After the mixture was stirred for 30min, chlorotrimethylsilane (1.86ml, 14.65mmol) was added dropwise and the mixture was allowed to come to room temperature for 1h. Most of THF was removed in vacuo, then n-pentane (15ml) was added and the precipitated salts removed by filtration. Evaporation of the filtrate under reduced pressure gave the mixture of the regioisomeric trimethylsilyl derivatives **16** and **17** which were utlilized in the next step without further purification.
To a solution of the crude mixture of **16** and **17** (2.28g) in acetonitrile (25ml) was added $Pd(OAc)_2$ (1.68g, 7.5mmol) and p-benzoquinone (0.4 g, 3.75mmol) and the mixture stirred at room temperature for 6h. Inorganic materials were removed by filtration and washed with EtOAc (2x20ml). The filtrate was concentrated in vacuo and the residue purified by column chromatography of silica gel (eluent: ether : light petroleum 2:3) to afford the enone **18** (0.9 g, 52%) as an oil, $[\alpha]^{D}_{22}$ = -101.7 (c, 1.05, $CHCl_3$): IR (neat): 1680 cm^{-1}; ^1H NMR: δ 0.96-0.93 (d, 3H, J=6.7), 2.35-2.57 (m, 3H), 2.74-2.89 (m, 1H), 3.54-3.58 (d, 2H, J=6.9), 4.53 (s, 2H), 6.01-6.07 (dd, 1H, J=2.3, J=10.2), 6.80-6.87 (dd, 1H, J=3.5, J=10.2), 7.31-7.36 (m, 5H) (Found: C, 78.19; H, 7.57. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88).and **19** (0.48g, 28%), $[\alpha]^{D}_{22}$ = +62.6 (c, 1.05, $CHCl_3$): IR (neat): 1680 cm^{-1}; ^1H NMR: δ 1.95-2.64 (m, 8H), 3.58-3.61 (d, 2H, J=5.6), 4.44-4.60 (AB system, 2H, J=3.58, J=3.61), 2H), 5.89 (sb, 1H), 7.31-7.36 (m, 5H). (Found: C, 78.09; H, 7.71. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88).

[3R-[3α(R*S*),4α,5α)]]-3-[1-Nitro-4-(1,3-dioxolan-2-yl)-butyl]-4-benzyloxymethyl-5-methylcyclohexanone 20.
Potassium tert-butoxide (0.15g, 2.7mmol) was added to a solution of 2-(3-nitrobutyl)-1,3-dioxolane (0.5g, 31.6mmol) and **18** (0.8g, 34.78mmol) in THF (20ml) and the mixture was stirred at room temperature for 36h. Most of the solvent was removed under vacuum and the residue partitioned between EtOAc (60ml) and water. The organic solution was separated, dried and concentrated under reduced pressure. The residual oil was purified by column chromatography (eluent : ether : light petroleum 3:2) to afford **20** as an oil (1.1g, 83%): IR (neat): 1720, 1560, 1340 cm^{-1}; ^1H NMR: δ 0.91-0.96 (m, 3H), 1.63-2.56 (m, 9H), 3.68-3.95 (m, 6H), 4.45-4.88 (m, 4H), 7.28-7.38 (m, 5H). (Found: C, 64.29; H, 7.41; N, 3.54. $C_{21}H_{29}O_6N$ requires C, 64.43; H, 7.47; N, 3.58).

[1S-(1α,2α,8αβ,8aα)]-1-Benzyloxymethyl-2-methyl-8-nitro-1,2,6,7,8,8a-hexahydro-[3H]-naphthalen-4-one 21.
A solution of the adduct **20** (0.43g, 1.1mmol) in EtOH (20ml) containing 5% HCl (0.5ml) was heated under reflux for 2.5h. The cooled mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with EtOAc (3x25ml). Evaporation of the dried organic extracts under vacuum gave the oily mixture of diastereomers **21** (0.22 g, 60.8%): IR (neat): 2900, 1640, 1560 cm^{-1}; ^1H NMR: δ 0.92-0.95 (d, 3H, J=6.83), 1.94-2.60 (m, 8H), 2.91 (m, 1H), 3.60-3.62 (d, 2H), 4.51 (s, 2H), 5.09 (m, 1H), 6.87 (m, 1H), 7.26-7.40 (m, 5H). (Found: C, 69.23; H, 6.96; N, 4.16. $C_{19}H_{23}O_4N$ requires C, 69.28; H, 7.04; N, 4.25).

[1S-(1α,2α,4αβ,8αβ,8aα)]-1-Benzyloxymethyl-2-methyl-8-nitro-1,2,3,4,6,7,8,8a-octahydronaphthalen-4-olo 22.

To a solution of **21** (0.33g, 1mmol) in methanol (50ml) containing $CeCl_3.6H_2O$ (0.55g, 1.57mmol) was added $NaBH_4$ (0.38g, 10mmol) and the mixture stirred for 10min at room temperature. Most of the methanol was removed in vacuum and the residue poured in water, extracted with EtOAc (3x25ml). Evaporation of the dried organic extracts under vacuum gave the oily mixture **22** (0.35g, 99.8%): IR (neat): 3600-3200, 1550, 1370 cm^{-1}; ^1H NMR: δ 0.84-1.68 (m, 5H), 1.80-2.34 (m, 7H), 3.01-3.08 (m, 1H), 3.39-3.49 (m, 2H), 4.09-4.49 (m, 3H), 4.90-5.02 (m, 1H), 5.70-5.92 (m, 1H), 7.23-7.38 (m, 5H). (Found: C, 68.59; H, 7.51; N, 4.14. $C_{19}H_{25}O_4N$ requires C, 68.86; H, 7.6; N, 4.23).

[1R-(1α,2α,4αβ,8αβ,8aα)]-1-Benzyloxymethyl-4-hydroxy-2-methyl-1,2,3,4,6,7-hexahydro-[8aH]-naphthalen-8-one 24.

To a cooled (0°C) solution of the nitroalcohol **22** (0.33g, 1mmol) in methanol (5ml) 30% hydrogen peroxide (2ml) and potassium carbonate (0.8g) in water (2.5ml) were added and the mixture stirred at room temperature for 15h. Acidification with 5% HCl gave a mixture of the expected ketone **24** (0.07g, 23%) and the corresponding oxime **23** (0.16g, 52%), which could be separated by filtration and crystallized, m.p. 172°C (MeOH); $[\alpha]^D_{22}$ = -141 (c, 0.62, $CHCl_3$); IR: 3600-3200, 1550,1370 cm^{-1}; ^1H NMR: δ 0.92-0.99 (m, 3H), 1.32-1.46 (dt, 1H), 1.82-2.52 (m, 6H), 3.16-3.52 (m, 4H), 4.26-4.46 (q, 2H), 4.77-4.80 (d, 1H, J=5.02), 5.58 (bs, 1H), 7.25-7.36 (m, 5H), 10.28-10.32 (m, 1H). (Found: C, 72.19; H, 7.71; N, 4.38. $C_{19}H_{25}O_3N$ requires C, 72.35; H, 7.99; N, 4.44).

A solution of **23** (0.3g, 0.95mmol) in 1:1 THF:H_2O (20ml) was treated with 15% aqueous $TiCl_3$ (3.36ml) and stirred at 60°C for 1h in the presence of ammonium acetate (1.68g). The cooled solution was filtered on Celite and extracted with EtOAc (3x20ml). The dried organic extracts were concentrated in vacuum to give the ketone **24** (0.20g, 72%). IR (neat): 3600-3200, 1715 cm^{-1}; ^1H NMR: δ 0.94-0.97 (d, 3H, J= 7.2), 1.95-2.77 (m, 6H), 3.16-3.52 (m, 9H), 3.28-3.47 (m, 2H), 4.13 (bs, 1H), 4.24-4.44 (m, 2H), 5.72 (bs, 1H), 7.25-7.33 (m, 5H). (Found: C, 75.89; H, 8.01. $C_{19}H_{24}O_3$ requires C, 75.97; H, 8.05).

[1R-(1α,2α,4αβ,8aα)]-1-Benzyloxymethyl-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-1,2,3,4,6,7-hexahydro-[8aH]-naphthalen-8-one 25.

To a solution of **24** (0.45g, 15mmol) in CH_2Cl_2 (20ml) Et_3N (0.42ml, 30mmol), ter-butyldimethyllsilylchloride (0.45g, 30mmol) and a catalytic amount of 4-(dimethylamino)pyridine were added and the mixture stirred at room temperature for 24h. The reaction mixture was poured in water, the organic layer separated and dried. Evaporation of the solvent gave an oily product which was purified by flash chromatography (ether : light petroleum 1:9) to give **25** (0.51g, 80%) as an oil, $[\alpha]^D_{22}$ = -48.95 (c, 0.56, $CHCl_3$): IR (neat) : 1720 cm^{-1}; ^1H NMR: δ 0.06-0.11 (m, 6H), 0.78-1.04 (m, 12H), 1.54-2.80 (m, 9H), 3.35-3.51 (m, 2H), 4.07-4.18 (m, 1H), 4.23-4.42 (q, 2H), 5.69 (m, 1H), 7.21-7.33 (m, 5H). (Found: C, 72.39; H, 9.11. $C_{25}H_{38}O_3Si$ requires C, 72.41; H, 9.24).

[1R-(1α,2α,4αβ,8β,8aα)]-1-Benzyloxymethyl-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-4-ol 26.

To a cooled (0°C) slurry of lithium aluminum tri-tert-butoxide hydride (0.5g, 13.3mmol) in THF (5ml) a solution of **25** (0.5g,12.1mmol) in THF (5ml) was added dropwise and the mixture stirred at room temperature for 6h. The reaction was quenched by careful addition of water and inorganic materials were removed by filtration. After evaporation of the organic filtrate, the crude product was purified by flash chromatography (eluent: ether : light petroleum 1:1) to give **26** (0.37g, 75%) as an oil, $[\alpha]^D_{22}$ = +28.8 (c, 0.43, $CHCl_3$); IR (neat): 3600-3300 cm^{-1}; ^1H NMR: δ 0.04-0.11 (m, 6H), 0.68-0.98 (m, 12H), 1.38-2.60 (m, 9H), 3.35-3.79 (m, 3H), 3.91-4.24 (m, 2H), 4.53 (s, 2H), 5.85-5.93 (m, 1H), 7.28-7.41 (m, 5H). (Found: C, 71.89; H, 9.51. $C_{25}H_{40}O_3Si$ requires C, 72.06; H, 9.68).

[1S[1α(S*),5αβ,7β,8β,8aβ]]-2-Methylbutanoic acid 8-benzyloxymethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthalenyl ester 27.

To a cooled (0°C) solution of the silyl alcohol **26** (0.34g, 82mmol) in CH_2Cl_2 (20ml) (S)-2-methylbutyric acid (0.09ml, 82mmol), dicyclohexylcarbodiimide (1.35g, 65.6mmol) and a catalytic amount of 4-(dimethylamino)pyridine were added and the mixture stirred at room temperature for 24h. The precipitated solid was removed by filtration, the filtrate evaporated in vacuum to give an oily product which was purified by flash chromatography (eluent: ether : light petroleum 1:9) to afford **27** (0.35g, 85%) as an oil, $[\alpha]^D_{22}$ = +38.5

(c, 0.4, $CHCl_3$); IR (neat): 1725 cm^{-1}; ^1H NMR δ 0.06-0.09 (m, 6H), 0.79-2.48 (m, 30H), 3.25-3.48 (m, 2H), 4.13-4.55 (m, 3H), 5.10-5.18 (m, 1H), 5.78-5.88 (m,1H), 7.20-7.38 (m, 5H). (Found: C, 71.79; H, 9.51 $C_{30}H_{48}O_4Si$ requires C, 71.95; H, 9.66).

[1S[1α(S*),5αβ,7β,8β,8aβ]]-2-Methylbutanoic acid 8-benzyloxymethyl-5-hydroxy-7-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthalenyl ester 28.

A solution of **27** (0.2g, mmol) in THF (5ml) was stirred at room temperature for 24h in the presence of a little amount of p-toluensulfonic acid. Solid $NaHCO_3$ was added, the solvent evaporated in vacuum and the residue was purified by flash chromatography (eluent: ether : light petroleum 1:1) to afford **28** (0.11, 68%) as an oil: IR: 3600-3300, 1725 cm^{-1}; ^1H NMR: δ 0.76-2.42 (m, 22H), 3.22-3.63 (m, 2H), 4.09-4.58 (m, 3H), 5.09-5.20 (m, 1H), 5.65-5.89 (m,1H), 7.27-7.35 (m, 5H). (Found: C, 74.49; H, 8.81. $C_{24}H_{34}O_4$ requires C, 74.58; H, 8.87).

[1S[1α(S*),7β,8β,8aβ]]-2-Methylbutanoic acid 8-benzyloxymethyl-1,2,3,7,8,8a-hexahydro-7-methyl-naphthalenyl ester 29.

To an ice-cooled solution of **28** (0.2g, 52 mmol) in pyridine (5ml) was added dropwise methansulfonyl chloride (0.4ml, 52mmol) and the mixture stirred for 4h at the same temperature. The mixture was poured in water (10ml), extracted with EtOAc (3x20ml), the extracts washed sequentially with 5%HCl and brine, then dried and evaporated in vacuum. Flash chromatography of the residue (eluent: ether : light petroleum 1 :1) gave **29** (0.13g, 68%) as an oil: IR (neat): 1730 cm^{-1}; ^1H NMR: δ 0.84-2.7 (m, 19H), 3.38-3.63 (m, 1H), 4.35-4.58 (m, 2H), 5.17 (bs, 1H), 5.56 (bs, 1H), 5.70-5.77 (dd, 1H, J=9.6, J=5.8), 5.94-5.99 (d, 1H, J= 9.7), 7.26-7.35 (m, 5H), contaminated by unseparable trace amounts of the rearranged diene **30**.

[1S[1α(S*),7β,8β,8aβ]]-2-Methylbutanoic acid 8-hydroxymethyl-1,2,3,7,8,8a-hexahydro-7-methyl-naphthalenyl ester 3.

To a solution of crude **29** (0.04 g, 0.11mmol) in dry CH_2Cl_2 (5ml) at -78°C was added boron trichloride (0.7ml of a 1M solution in hexanes, 0.7mmol) and the mixture stirred for 3h, then poured into phosphate buffer (8ml) and stirred at room temperature for 2h. Extraction with EtOAc (3x15ml), followed by washing with brine and evaporation of the dried extracts, gave a residue, which was purified by column chromatography (eluent: ether: light petroleum 2:3) to give **3** (0.012g, 40%) as a solid, m.p.64-65°C, identical in all respects with the compound described by Heathcock.[2b]

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References and Notes.

#. Dedicated to Prof. Giorgio Traverso on the occasion of his retirement.

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* In order to be more confident of the absolute configuration of the chiral centers in **10** to be 1S,3S and 4S and at the same time to have an estimate of the optical purity, (-)-**10** has been transformed into *cis*-(3S,4R)-3,4-dimethylcyclohexan-1-one by a three step sequence involving selective tosylation of the primary hydroxyl group by action of p-toluensulfonyl chloride in pyridine to afford the monotosylate, followed by reduction with $LiAlH_4$ to 3,4-dimethylcyclohexanol , eventually converted by Jones oxidation to the known ketone, $[\alpha]_D^{20}$ = -13.5, e.e. = 91%: Milhavet ,J. C.; Sablayrolles, C.; Girard, J. P.; Chapat, J. P., *J. Chem. Res. (S)*, **1980**, 134-135.
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