Tetrahedron Asymmetry Vol 2, No 2, pp 123-138, 1991
Printed in Great Britain

0957-4166/91 $3 00+ 00
Pergamon Press plc

Resolution and EPC Synthesis of Both Enantiomers of 2,5-Dimethylbicyclo[3.2.0]heptan-*endo*-2-ol, Key Intermediate in the Synthesis of Grandisol.

Goffredo Rosini,* Emanuela Marotta, Andrea Raimondi and Paolo Righi

Dipartimento di Chimica Organica *A.Mangini* dell'Università
Viale Risorgimento, 4 - I-40136 Bologna (Italy)

(*Received* 3 *January* 1991)

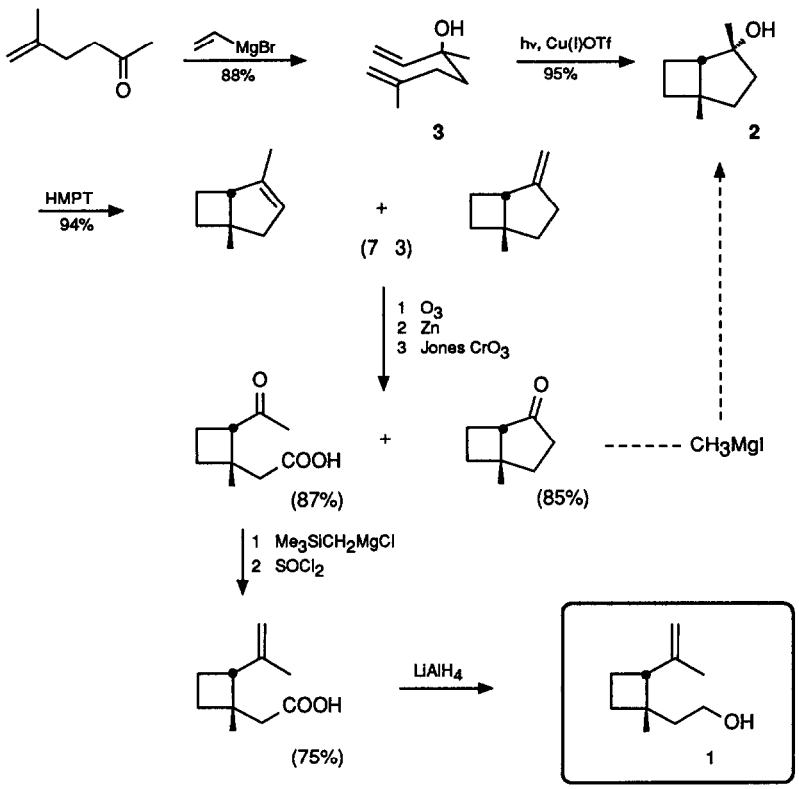
Abstract. The pure enantiomers of 2,5-dimethylbicyclo[3 2 0]heptan-*endo*-2-ol, key intermediate in the synthesis of grandisol, have been conveniently prepared by optical resolution with (2S)-(–)- and (2R)-(+)-1-(4-toluenesulphonyl)pyrrolidine-2-carboxylic acid chloride (NTP-Cl) as resolving agents, and by an EPC synthesis employing commercially available (3R)-(–)- and (3S)-(+)-linalool as chiral sources

In 1969, *cis*-2-isopropenyl-1-methylcyclobutaneethanol (**1**), named "grandisol", was identified[1] as the major component of the four synergistic constituents of "grandlure", the sex pheromone of male cotton boll weevils, *Anthonomus grandis* Boheman, an important pest of cotton crops in the U S A More recently, it has been found that grandisol is also released by females of the ambrosia beetle *Trypodendron signatum* L ,[2] by males of bark beetles *Pityophthorus pityographus*,[3] of *Pityogenes quadridens*[4] and of *P calcaratus*,[4] while grandisol and the respective aldehyde, grandisal, have been identified as pheromones of *Pissodes* weevils [5] Therefore, today it is possible to claim that grandisol can be considered a "word" present in many insect "languages" inducing behavioural responses in several different species

The elegant synthesis of Hobbs and Magnus[6] starting from (–)-β-pinene assigned the (1R,2S)-stereochemistry to (+)-grandisol, the natural enantiomer component of grandlure Since then, several EPC syntheses[7] of both enantiomers of grandisol[8-15] have been developed enabling entomologists to study the stereochemistry-pheromone activity relationship However, a critical examination of the reported preparations of the pure enantiomers of grandisol reveals that they are obviously not economically viable and do not open the way to the application of newer methods of surveying and controlling pest insects in agriculture

Now, we wish to present successful preparations of pure enantiomers of 2,5-dimethylbicyclo[3 2 0] heptan-*endo*-2-ol (2), key intermediate in the synthesis of grandisol

In 1985 we reported[16] a highly efficient and practical synthesis of racemic grandisol in which all carbon atoms of the target molecule were derived from readily available and inexpensive starting materials (*Scheme I*) This six-step procedure provides (±)-grandisol in 42% overall yield based on



Scheme I

5-methyl-5-hexen-2-one[17] and necessitates a minimum of intermediate purification In this synthesis, the dienol **3** has only one chiral centre, the same chiral centre that we find on bicyclic alcohol **2** which is lost during the dehydrating reaction It is worth noting that the copper(I)-catalyzed[18] photobicyclization of dienol **3** occurs in a stereospecific fashion and that the chiral centre of **3** induces the formation of two additional and adjacent chiral centres in compound **2** These two chiral centres are retained through the whole process and can be found unchanged in grandisol

The bicyclic alcohol **2** seemed to be an ideal candidate for optical resolution and recently we achieved successful resolution of enantiomers of **2** *via* the diastereoisomeric camphanates [19] Here it was possible to determine the specific rotations and to assign the (1S,2R,5S)- and the (1R,2S,5R)-

configuration to (+)-**2** and (–)-**2** respectively

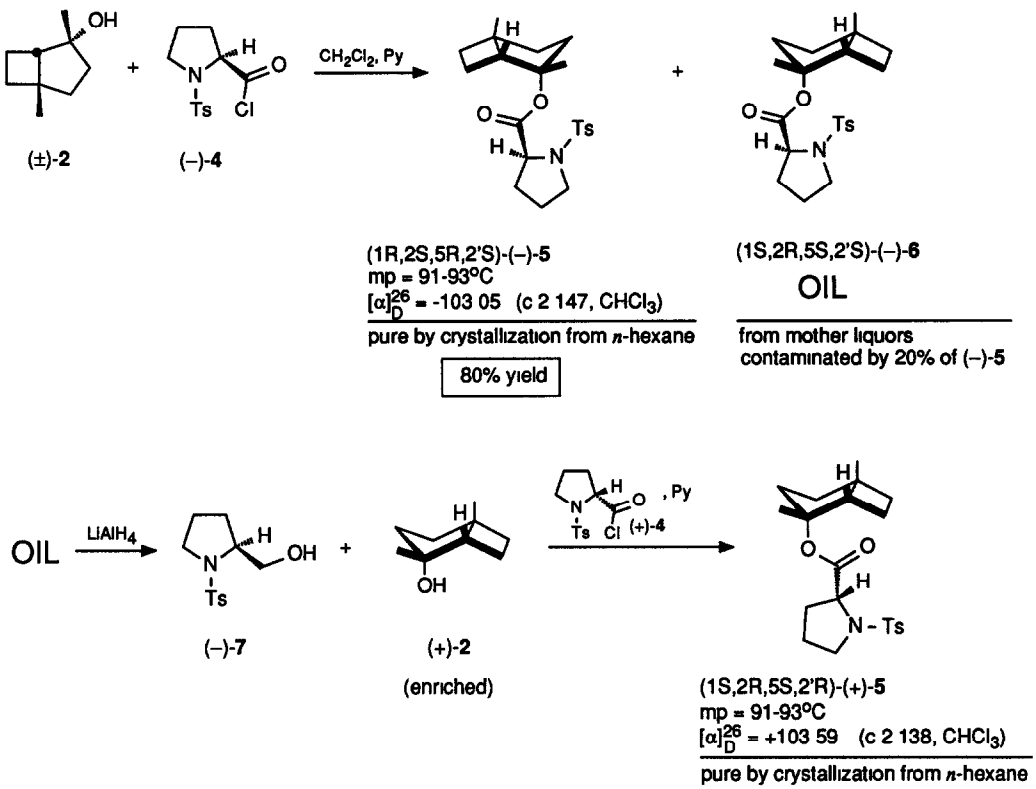
RESULTS AND DISCUSSION.

With these results in hand we oriented our efforts toward the preparation of enantiomerically pure (+)-**2** and (–)-**2** by following two classical approaches

Optical Resolution of **2** - The utilization of (1S)-(–)-camphanic acid chloride[20] as resolving agent allowed us to obtain small samples of enantiomeric pure (+)-**2** and (–)-**2** and to elucidate the optical properties of these compounds [19] However, fractional crystallization of diastereoisomeric camphanates of **2** proved to be difficult and time consuming Moreover, camphanic acid cannot be reused since the reductive cleavage of pure diastereoisomers also cleaves the lactone ring, and the stoichiometric consumption of this resolving agent cannot be considered viable in a process desired to be run on an economic scale Having observed the clear limits of our previous procedure, we chose proline as the lead compound for the synthesis of chiral auxiliaries to continue the task of optical resolution of **2** whilst looking for a more convenient method Our choice is based on two main observations (a) both enantiomers of proline are commercially available α-amino acids with high enantiomeric purity,[21] (b) this chiral pyrrolidine possesses two important functional groups, both on the same carbon atom, the chiral centre, which is involved in the ring system While the carboxylic group is necessary for the esterification, the amino group could be used to finely tune the physico-chemical properties of ester diastereoisomers to be separated *via* appropriate modifications Because of these features, (2S)- and (2R)-proline are suitable substrates to obtain several chiral 1-substituted derivatives available in esterification with racemic alcohols for their conversion into diastereoisomers

Starting from (2S)-proline we prepared several differently substituted 1-benzenesulphonylpyrrolidine-2-carboxylic acids by a simple and efficient procedure [22] Esterification of **2** with these 1-substituted (2S)-proline derivatives without racemizing the 2-pyrrolidine carboxylic acid moiety was best achieved by using the corresponding acid chlorides prepared with oxalyl chloride in dry benzene

This systematic approach allowed us to identify (2S)-1-(4-toluenesulphonyl)pyrrolidine-2-carboxylic acid chloride [(2S)-NTP-Cl, **4**] as an apt resolving agent for a practical and inexpensive resolution of compound **2** (*Scheme II*) In fact, only one crystallization of diastereoisomeric (2S)-NTP-esters of **2** with *n*-hexane was sufficient to obtain a crystalline compound in 80% yield A further crystallization in *n*-hexane furnished levorotating pure **5** without relevant loss of material By evaporation of mother liquors we obtained a viscous oil containing the other diastereoisomer (**6**) as the main component together with a residual 20% of (–)-**5** Lithium aluminum hydride reduction of this mixture gave (+)-enantiomer enriched **2** and (2S)-1-(4-toluenesulphonyl)prolinol [(–)-**7**] The enriched **2** was esterified with (2R)-(+)-NTP-chloride (**4**) and pyridine Again, a diastereisomeric mixture of esters was obtained that gave dextrorotating **5** in 95% yield by crystallization from *n*-hexane

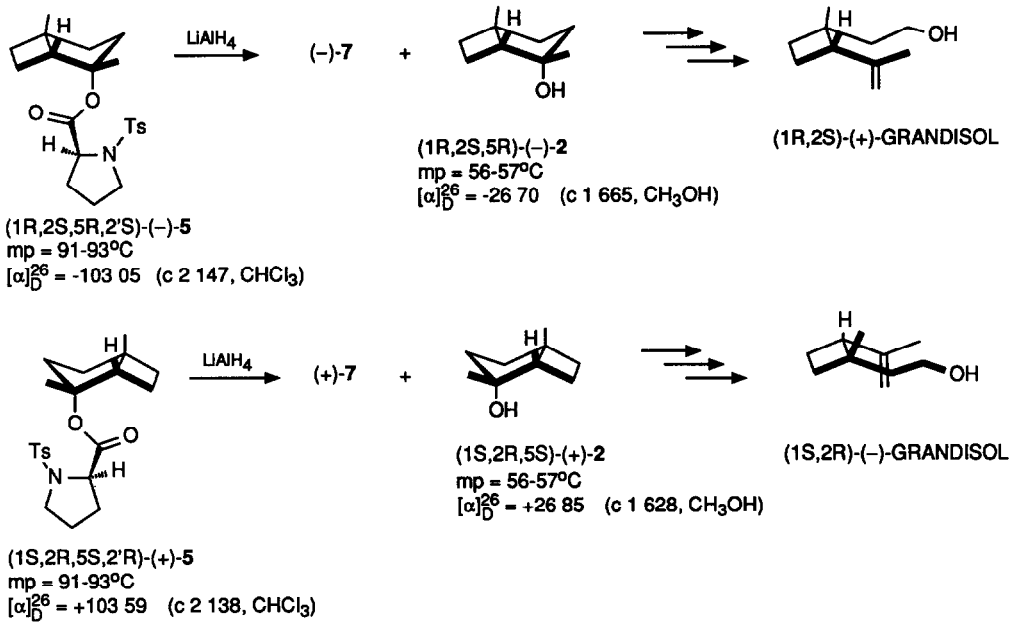


Scheme II

By this procedure we achieved an efficient separation of (+)- and (–)-**5** in good yields These enantiomers underwent separate lithium aluminum cleavage in tetrahydrofuran giving enantiomerically pure (1R,2S,5R)-(–)-**2** and (1S,2R,5S)-(+)-**2** in high yields together with 1-(4-toluenesulphonyl)prolinols (–)-**7** and (+)-**7** respectively (*Scheme III*) It is worth noting that these latter chiral reduction products can be easily converted into the corresponding optically active carboxylic acids by oxidation with Jones reagent[24] or with RuO_4-$NaIO_4$ [25]

The possibility to recover and reuse the resolving agents without loss of enantiomeric purity make our procedure particularly economical as well as practical and efficient

The reaction of pure (1S,2R,5S)-(+)-**2** with (2S)-(–)-NTP-Cl (**4**) gave pure (1S,2R,5S,2'S)-(–)-**6**, which has an enantiomeric relationship with (1R,2S,5R,2'R)-(+)-**6**, obtained by reaction of pure (1R,2S,5R)-(–)-**2** with (2R)-(+)-NTP-Cl (**4**), so that we are aware of the physico-chemical and spectroscopic properties of these more soluble diastereoisomers having lower melting points with respect to compounds **5** It should be noted that in spite of the easy separation of **5** from its diastereoisomer **6**



Scheme III

by a simple crystallization, these two esters are almost undistinguishable from a spectroscopical point of view ^{1}H NMR spectra of **5** and **6** are quite similar although small, but useful differences, were observed between their IR(KBr) spectra ester carbonyl of **5** reveals a sharp and strong signal at ν 1747 cm^{-1} whereas ester **6** shows this signal at ν 1739 cm^{-1} However, the two signals of the ^{13}C NMR spectra of **5** and **6** can be considered as diagnostic at δ 51 84 and at δ 61 04 ppm for **5** and at δ 51 99 and at δ 61 17 ppm for **6**

Every attempt performed by using 1-(benzenesulphonyl)-, 1-(3,5-dimethylbenzesulphonyl)-, and 1-(4-nitrobenzenesulphonyl)-pyrrolidine-2-carboxilic acid chloride as resolving agents gave mixtures more difficult to separate by crystallization

The "Chiron" Approach [26]- Synthesis of optically active natural products using naturally occurring optically active materials is the most efficient way when they are available and adaptable Therefore, finding common chiral pools adaptable to versatile target molecules is an important task in organic synthesis We have exploited the considerable structural analogy between dienol **3** and linalool (*Fig 1*) The monoterpene alcohol linalool occurs in nature in both dextrorotatory (coriandol) and levorotatory (licareol) forms as constituents of essential oils [27,28] Moreover, these enantiomers can be prepared from α-pinenes by an industrial procedure devised by Ohloff *et al* [29] that gives (+)- and (−)-linalool with optical purities greater than 93%

In 1982 Magnus reported[30] a very efficient and selective preparation of 4-methyl-4-trimethyl-

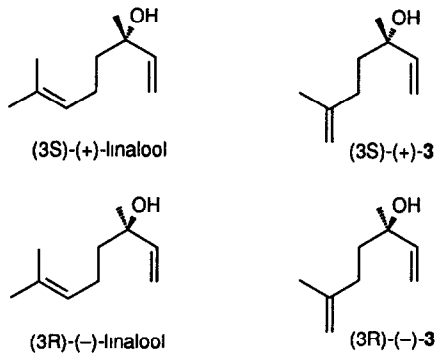
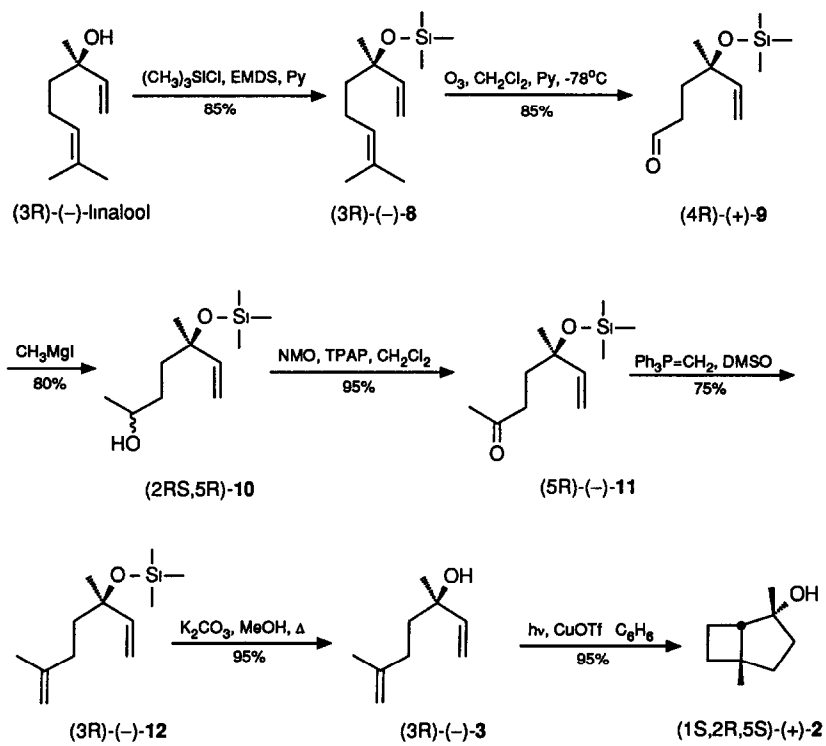


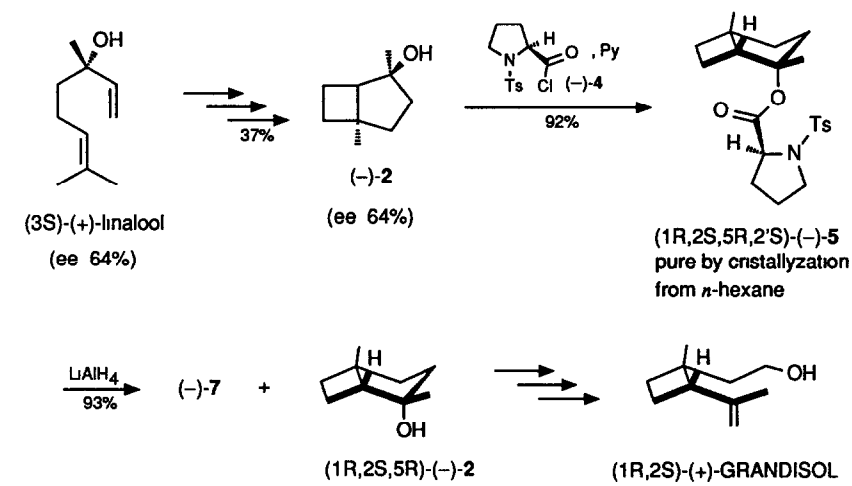
Fig. 1

silyloxyhex-5-enal (**9**) in the conversion of (3R)-(−)-linalool into (R)-(+)-frontalin Stimulated by these findings we used commercial (3R)-(−)-linalool (ee ≥ 96%) and (3S)-(+)-linalool (ee ≈ 60%) as chiral starting materials[31] in our EPC synthesis of (+)-**2** and (−)-**2** respectively Scheme IV shows how (3R)-



Scheme IV

(–)-**3** was gained from manipulation of (3R)-(–)-linalool The procedure consists of an initial selective and efficient oxidative cleavage of the peripheral double bond followed by a remaking of the olefinic moiety to obtain the right residue for the final conversion into enantiomerically pure (1S,2R,5S)-(+)-**2**, precursor of (1S,2R)-(–)-grandisol, by stereospecific copper(I)-catalyzed $2\pi+2\pi$ photobicyclization This synthetic sequence was achieved in 37% overall yield starting from linalool The same reaction sequence gave (1R,2S,5R)-(–)-**2** (ee 64%) when we used (3S)-(+)-linalool with the same enantiomeric excess However, this enriched levorotating sample of **2** has been purified by esterification with (2S)-(–)-NTP chloride **4** and crystallization of the major diastereisomeric component (–)-**5** from *n*-hexane (*Scheme V*) This pure derivative was reductively cleaved by reaction with lithium aluminum hydride Enantiomerically pure (1R,2S,5R)-(–)-**2** was obtained in 27% overall yield, and can be converted into (1R,2S)-(+)-grandisol



Scheme V

It must be pointed out that to prepare (+)-grandisol, the enantiomer of grandisol naturally occurring in grandlure, the less expensive enantiomer of proline, the (2S)-(–)-proline, is required for the purification This fact counterbalances the lower optical purity of (3S)-(+)-linalool commercially available

CONCLUSIONS.

The resolution procedure and the EPC synthesis we have just described leads to the obtainment of both enantiomers of 2,5-dimethylbicyclo[3 2 0]heptane-*endo*-2-ol (**2**) enantiomerically pure in high yields Since this latter has previously been converted to grandisol[19,32] avoiding racemization during the process, our work constitutes a formal EPC synthesis of this pheromone component The experimen-

tal conditions described herein are generally not sensitive to small changes and they consistently meet the requirements for large scale preparations

At the beginning of this article we anticipated that grandisol is present in other pheromone blends Consequently, the synthetic routes developed in this research will also be useful to prepare pheromone blends of the other insects cited previously

EXPERIMENTAL SECTION

Melting and boiling points are uncorrected Infrared spectra were recorded as oil films unless otherwise stated, on a Perkin-Elmer 983 G instrument ^{1}H NMR spectra in $CDCl_3$ solution were recorded on a Varian Gemini spectrometer operating at 200 MHz using tetramethylsilane (TMS) or $CHCl_3$ as internal standard ^{13}C NMR were recorded in $CDCl_3$ solution at 50 30 MHz with a Varian Gemini spectrometer by the FT technique Microanalyses were determined by using C,H,N Analyzer Model 185 from Hewlett-Packard Co Precoated silica gel plates Merck Kieselgel 60 F_{254} were used for analytical thin layer chromatography (t l c) Merck Kieselgel 60 was employed for flash column chromatography Reactions were performed using purified and dried solvents under an atmosphere of nitrogen Light petrol ether (40-60°C fraction) was used and referred to as petrol ether Optical rotations were measured on a Jasco DIP-360 polarimeter equipped with a sodium light source Densities of neat liquids were determined at 25°C Irradiations were conduced under dry nitrogen in a cylindrical Pyrex vessel with a quartz water-cooled double-walled immersion well Reaction mixtures were stirred magnetically and irradiated internally with a Hanovia medium pressure 450-W mercury vapor lamp (2S)-, (2R)-Proline and copper(I)trifluoromethanesulphonate-benzene complex were obtained from Fluka (3R)-(–)-Linalool and (3S)-(+)-linalool were obtained from K&K Laboratories and were further purified by spinning band distillation

Optical resolution of (–)-2,5-Dimethylbicyclo[3.2.0]heptan-*endo*-2-ol (2).

Preparation of 1-(4-Toluenesulphonyl)-2-pyrrolidylcarboxylates **(1R,2S,5R,2'S)-(–)-5** *and* **(1S,2R,5S,2'R)-(+)-5**

A solution of (2S)-(–)-1-(4-toluenesulphonyl)prolyl chloride[22,23] (NTP-chloride, **4**, 20 53 g, 71 mmol) in dichloromethane (125 ml) and dry pyridine (8 5 ml, 106 mmol) was dropped into an ice-cold, stirred solution of (±)-**2**[16,19] (10 0 g, 71 mmol) dissolved in dichloromethane (125 ml) The mixture was stirred at room temperature for 5 h, washed with 1N hydrochloric acid (2x60 ml) and with a saturated aqueous sodium bicarbonate solution Finally the dichloromethane solution was dried (Na_2SO_4) and the evaporation of the solvent gave a colorless oil The oil was dissolved in dichloromethane, passed through a short column of silica gel and recovered (26 1 g, 94% yield) by

evaporation of the solvent at reduced pressure Crystallization of this oil from *n*-hexane (150 ml) with few milliliters of diethyl ether afforded colorless white crystals of **(1R,2S,5R,2'S)-(–)-5** (11 12 g, 80 1%). mp 91-93°C, $[\alpha]_D^{26}$ -103 05 (c 2.147, chloroform), IR (KBr disk) ν 1747, 1600, 1344, 1161 cm^{-1}, ^1H NMR δ 1 15-2 70 (4H, m), 1 17, 1 37, 2 43 (3H each, s each, methyls), 3 25-3 4 (1H, m), 3 40-3 53 (1H, m), 4 0-4 4 (1H, m), 7 2 (2H, d, J=8 0Hz), 7 7 ppm (2H, d, J=8.0Hz), ^{13}C NMR δ 14 90, 21 64, 24 21, 24 79, 27 96, 30 79, 31 38, 37 08, 37 78, 42 88, 48 52, 51 84, 61 04, 89 57, 128 01, 130 02, 136 44, 143.85, 171 68 ppm

Anal Calcd for $C_{21}H_{29}NO_4S$ C,64 43, H,7 47, N,3 58 Found C,64 41, H,7.37, N,3 61

Mother liquors were concentrated to give a crude diastereoisomeric mixture (14 98 g, 38 mmol) which was dissolved in dry tetrahydrofuran (THF, 80 ml) and slowly added to a stirred suspension of $LiAlH_4$ (5 0 g) in THF (150 ml) The reaction mixture was left under stirring at room temperature for 5 h Upon completion of the reaction (t l c control), the mixture was cooled at 0°C, diethyl ether (200 ml) was added, and a saturated aqueous solution of NH_4Cl was dropped to destroy the hydride in excess The organic phase was separated, washed three times with water (20 ml), dried (Na_2SO_4) and evaporated at reduced pressure Washings of this residue with cold diethyl ether (3x30 ml) allowed a rough but efficient separation of the very soluble enriched (+)-**2** from (2S)-(–)-1-tosylpyrrolidyl-2-methylalcohol [(–)-**7**] This latter was collected as a white solid· mp 90-91°C from Et_2O, $[\alpha]_D^{26}$ -89 8 (c 1 70, methanol), lit [22,23] mp 88-89°C from Et_2O, $[\alpha]_D^{26}$ -92 0 (c 1 0, chloroform) Enriched (+)-**2** was obtained pure (4 97 g, 93%) by flash column chromatography,[33] with petrol ether/diethyl ether (4 1) as eluent Successive elution with diethyl ether allowed the recovery of residual (–)-**7**

The purified enriched (+)-**2** (4 0 g, 28 5 mmol) was treated with (2R)-(+)-NTP-chloride (**4**, 8 2 g, 28 5 mmol) according to the just described procedure for racemic **2** The work-up of the reaction mixture and crystallization gave **(1S,2R,5S,2'R)-(+)-5** (7 18 g, 82%) mp 91-93°C, $[\alpha]_D^{26}$ +103 59 (c 2 138, chloroform), spectroscopic data (IR, ^1H and ^{13}C NMR) are identical with those of **(1R,2S,5R,2'S)-(–)-5**

Anal Calcd for $C_{21}H_{29}NO_4S$ C,64 43, H,7 47, N,3 58 Found C,64.41, 7 38, N,3 61

Reductive Cleavage of Esters **(–)-5** *and* **(+)-5**

Ester (–)-**5** (5 0 g, 12 7 mmol) was treated with $LiAlH_4$ (1 0 g) in dry THF according to the procedure to obtain the enriched (+)-**2** described before Washings of the residue with cold diethyl ether (2x20 ml) gave **(2S)-(–)-7** as a white solid· mp 90-91°C from Et_2O, $[\alpha]_D^{26}$ -89 8 (c 1 70, methanol) The ethereal solution was evaporated and the residue was purified by flash column chromatography eluing with petrol ether-diethyl ether (4·1) The fractions containing pure (–)-**2** were collected and the evaporation of the solvent gave (1R,2S,5R)-(–)-2,5-dimethylbicyclo[3 2 0]heptan-*endo*-2-ol **[(1R,2S,5R)-(–)-2]**, (1 65 g, 93%) mp 56-57°C from ethanol-water and successive sublima-

tion at 65°C/15mmHg, $[\alpha]_D^{26}$ -26 70 (c 1 665, methanol), lit [19] mp 56-57°C, $[\alpha]_D^{23}$ -26 40 (c 1 622, methanol)

Anal Calcd for $C_9H_{16}O$ C,77 09, H,11 50 Found C,77 15, H,11 68

Ester (+)-**5** (5 0 g, 12 7 mmol) was treated in an analogous way and the same work-up of the reaction mixture just described for ester (–)-**5** gave (**2R**)-(+)-**7** (3 07 g, 93%) as a white solid mp 90-91°C from Et_2O, $[\alpha]_D^{26}$ +89 81 (c 1 726, methanol) and (1S,2R,5S)-(+)-2,5-dimethylbicyclo[3 2 0]heptan-*endo*-2-ol [(**1S,2R,5S**)-(+)-**2**], (1 60 g, 90%) mp 56-57°C from ethanol-water and successive sublimation at 65°C/15mmHg, $[\alpha]_D^{26}$ +26 85 (c 1 628, methanol), lit. [19] mp 56-57°C, $[\alpha]_D^{23}$ +26 79 (c 1 630, methanol)

Anal Calcd for $C_9H_{16}O$ C,77 09, H,11 50 Found C,76 85, H,11 23

The spectroscopic data of (–)-**2** and (+)-**2** were identical with those of the racemic compound previously reported [16]

Preparation of 1-(4-Toluenesulphonyl)-2-pyrrolidylcarboxylates (**1S,2R,5S,2'S**)-(–)-**6** *and* (**1R,2S,5R,2'R**)-(+)-**6**

(2S)-(–)-NTP-Cl[22,23] (**4**, 5 78 g, 20 mmol) and (**1S,2R,5S**)-(–)-**2** (2 52 g, 18 mmol) were treated in dichloromethane (50 ml) and dry pyridine (3 ml) as described previously for the preparation of (–)-**5** Work-up of the reaction mixture gave (**1S,2R,5S,2'S**)-(–)-**6** (6 69 g, 95%) mp 74-76°C, $[\alpha]_D^{26}$ -43 80 (c 2 180, chloroform), IR (KBr) ν 1739, 1600, 1333, 1150 cm^{-1} , ^1H NMR δ 1 20-2 60 (4H, m), 1 18, 1 35, 2 43 (3H each, s each, methyls), 3 25-3 40 (1H, m), 3 40-3 52 (1H, m), 4.20-4 28 (1H, m), 7 32 (2H,d, J=8 0Hz), 7 75 ppm (2H, d, J=8 0Hz), ^{13}C NMR δ 14 99, 21 63, 24 16, 24 79, 27 94, 30 77, 31 16, 37 08, 37 81, 42 90, 48 57, 51 99, 61 17, 89 54, 127 95, 130 04, 136 44, 143 85, 171 58 ppm

Anal Calcd for $C_{21}H_{29}NO_4S$ C,64 43, H,7 47, N,3 58 Found. C,64 54, H,7 61, N,3 35

The esterification of (**1R,2S,5R**)-(+)-**2** with (2R)-(+)-NTP-chloride **4** gave (**1R,2S,5R,2'R**)-(+)-**6** in 94% yield mp 74-76°C, $[\alpha]_D^{26}$ +43 75 (c 2 168, chloroform) Its IR, ^1H and ^{13}C NMR spectra were identical with those of (**1S,2R,5S,2'S**)-(–)- **6**

Anal Clacd for $C_{21}H_{29}NO_4S$ C,64 43, H,7 47, N,3 58 Found C,63 57, H,7 61, N,3 42

(3R)-3,7-Dimethyl-3-trimethylsilyloxyoct-1,6-diene [(**3R**)-(–)-**8**] (3R)-(–)-Linalool (ee ≥ 98%,[31] 20 0 g, 130 mmol) in dry pyridine was treated with hexamethyldisilazane (HMDS, 33 ml, 158 mmol) and then with chlorotrimethylsilane[30] (9 0 ml, 71 mmol) After 24 h at 20°C the mixture was filtered through Celite eluing with diethyl ether The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (2x30 ml), dried ($MgSO_4$) and evaporated The residue was distilled at reduced pressure to give the protected linalool (**3R**)-**8** (25 g, 85%) bp 60-64°C/1 0mmHg (lit [30]45°C/0 17mmHg), $[\alpha]_D^{26}$ -

4 35 (d 0 839), IR ν 2950, 1450, 1370, 1250, 1175, 920 cm^{-1}, ^1H NMR δ 0 1 (9H, s), 1 3 (3H,s), 1 5 (6H, d, J=4 0Hz), 1 40-1 55 (2H, m), 1 9-2 1 (2H, m), 4 9-5 2 (2H+1H, m), 5 8-5.9 ppm (1H,m)

Anal Calcd for $C_{13}H_{26}OSi$ C,68 95, H,11 57 Found C,69 12, H,11 71

(3S)-3,7-Dimethyl-3-trimethylsilyloxyoct-1,6-diene **[(3S)-(+)-8]** In the same manner as described above (3S)-(+)-linalool (ee ≈ 60%,[31] 20 0 g, 130 mmol) was converted into **(3S)-8** bp 60-64°C/ 1 0mmHg, $[\alpha]_D^{26}$ +2 45 (d 0 839) Its IR and ^1H NMR spectra were identical with those of **(3R)-8.**

Anal Calcd for $C_{13}H_{26}OSi$ C,68 95, H,11 75 Found C,69 15, H,11 67

(4R)-4-Methyl-4-trimethylsilyloxyhex-5-enal **[(4R)-(+)-9]** Trimethylsilylether of (3R)-linalool, **[(3R)-8**, 12g, 53 mmol] was dissolved in dichloromethane (250 ml) and dry pyridine (5 0 ml, 62 mmol), and then cooled at -78°C The reaction mixture was treated with ozone until the disappearance of starting material (ca 2h) The mixture was filtered through Celite into cold water (400 ml) containing dimethyl sulphide (8 0 ml) After one hour under magnetic stirring at room temperature the organic layer was separated, washed with water (2x70 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give an oil The oil was dissolved in diethyl ether, filtered through Celite, dried ($MgSO_4$) and distilled to give **(4R)-9** (9 03 g, 85%) bp 35-36°C/10mmHg (lit [30] bp 34-35°C/10 37mmHg), $[\alpha]_D^{26}$ +2 56 (d 0 899), IR ν 2961, 2819, 2719, 1729, 1250, 1152, 1042, 842 cm^{-1}, ^1H NMR δ 0 00 (9H,s), 1 25 (3H, s), 1 6-1 9 (2H, m), 2 2-2 4 (2H, m), 4 9-5 2 (2H, m), 5 60- 5 85 (1H, m), 9 65 ppm (1H, s)

Anal Calcd for $C_{10}H_{20}OSi$ C,65 14, H,10 93 Found C,65 28, H,10 78

(4S)-4-Methyl-4-trimethylsilyloxyhex-5-enal **[(4S)-(–)-9]** In the same manner as described above **(3S)-8** (12 0 g, 53 mmol) underwent selective ozonolysis to give **(4S)-9** bp 35-36°C/10mmHg, $[\alpha]_D^{26}$ -1 55 (d 0 899) Its IR and ^1H NMR spectra were identical with those of **(4R)-9.**

Anal Calcd for $C_{10}H_{20}OSi$ C,65.14, H,10 93 Found C,65 31, H,10 98

(2RS,5S)-5-Methyl-5-trimethylsilyloxyhept-6-en-2-ol **(10)** To a solution of methylmagnesium jodide prepared starting from methyl jodide (5 6 ml) and magnesium (2 2 g) in diethyl ether (80 ml), the aldehyde **(4R)-9** (12 0 g, 60 mmol) in diethyl ether (80 ml) was slowly added under stirring After the mixture was stirred for two hours at room temperature, few milliliters of a saturated aqueous solution of NH_4Cl were added and usual work-up of the reaction mixture gave **(2RS,5S)-10** as an oil (10 37g, 80%) IR ν 3366, 2966, 1251, 1045, 841 cm^{-1}, ^1H NMR δ 0 00 (9H, s), 1 04 (3H, d, J=6 2Hz), 1 2 (3H, s), 1.25-1 62 (4H, m), 2 54 (2H, m), 5 62-5 84 ppm (1H, m)

Anal Calcd for $C_{11}H_{24}O_2Si$ C,61 05, H,11 17 Found C,61 12, H,11 25

(2RS,5R)-5-Methyl-5-trymethylsilyloxyhept-6-en-2-ol (**10**) In a like manner alkylation of **(4S)-9** gave the corresponding alcohol **10** in a ca 80% yield IR and ^{1}H NMR spectra were identical with those of **(2RS,5S)-10.**

Anal Calcd for $C_{11}H_{24}O_2Si$ C,61 05, H,11 17 Found C,61 15, H,11 23

Both alcohols **10** were used in the next step without further purification

(5R)-5-Methyl-5-trimethylsilyloxyhept-6-en-2-one [**(5R)-(–)-11**] The alcohol **(2RS,5S)-10** (5 00 g, 23 1 mmol) dissolved in dichloromethane (60 ml) was added to a solution of N-methyl morpholine N-oxide monohydrate (NMO, 4 80 g, 35 5 mmol) in dichloromethane (150 ml) containing both 4Å sieves (7 0 g) and tetra-*n*-propylammonium *per*-ruthenate[34](TPAP, 0 35 g, 1 0 mmol) The reaction was followed by t l c eluing with petrol ether-diethyl ether (7 3) until complete The initial green mixture darkened as the reaction proceeded After half an hour the reaction can be considered complete The mixture was diluted with dichloromethane (100 ml), filtered to separate molecular sieves, and concentrated at reduced pressure The residue was dissolved with diethyl ether and filtered again to separate the catalyst The filtrate was evaporated at reduced pressure to give **(5R)-11** (4 70 g, 95%) as an oil sufficiently pure to be used in the next step Part of this sample was purified by flash column chromatography[33] eluing with petrol ether-diethyl ether (7 3) to give an oil $[\alpha]_D^{26}$ -1 86 (d 0 894), IR ν 2962, 1720, 1252, 1046, 841 cm^{-1}, ^{1}H NMR δ 0 05 (9H, s), 1 29 (3H, s), 1 65-1 82 (2H, m), 2 10 (3H, s), 2 35-2 48 (2H, m), 4 93-5 18 (2H,m), 5 68-5 84 ppm (1H, m)

Anal Calcd for $C_{11}H_{22}O_2Si$ C,61 62, H,10 34 Found C,61 71, H,10 41

(5S)-5-Methyl-5-trimethylsilyloxyhept-6-en-2-one [**(5S)-(+)-11**] The oxidation of **(2RS,5R)-10** (5 0g, 23 1 mmol) gave **(5S)-11** as an oil $[\alpha]_D^{26}$ -1 55 (d 8 94), spectrally identical with **(5R)-11**

Anal Calcd for $C_{11}H_{22}O_2Si$ C,61 62, H,10 34 Found C,61 75, H,10 45

(3R)-3,6-Dimethyl-3-trimethylsilyloxyhepta-1,6-diene [**(3R)-(–)-12**] The ketone **(5R)-11** (7 00g, 32 7 mmol) was added to methylenetriphenylphosphorane (30 0 mmol) prepared starting from methyltriphenylphosphonium bromide and sodium hydride in dimethyl sulphoxide [35] The reaction mixture was stirred at room temperature until the reaction was complete Then, water was added and the aqueous phase was ectracted with *n*-pentane (3x50 ml) The pentane fractions were washed with brine (3x10 ml) and dried ($MgSO_4$) Evaporation at reduced pressure followed by a fast column chromatography eluing with petrol ether gave pure **(3R)-12** (5 22 g, 75%) as an oil $[\alpha]_D^{26}$ -5 94 (d 0 850), IR ν 2966, 1252, 1051, 840 cm^{-1}, ^{1}H NMR δ 0 13 (9H, s), 1 34 (3H, s), 1 55-1 70 (2H, m), 1 73 (3H, s), 1 95-2 10 (2H, m), 4 68 (2H, bs), 4 95-5 22 (2H, m), 5 68-5 95 ppm (1H, m)

Anal Calcd for $C_{12}H_{24}OSi$ C,67 85, H,11 38 Found C,67 92, H,11 62

(3S)-3,6-Dimethyl-3-trimethylsilyloxyhepta-1,6-diene **[(3S)-(+)-12]** In a like manner methylenation of **(5S)-11** gave the corresponding diene **(3S)-12** in 75% yield $[\alpha]_D^{26}$ +3 75 (d 0.850). IR and ^{1}H NMR spectra were identical with those of **(3R)-12**

Anal Calcd for $C_{12}H_{24}OSi$ C,67 85, H,11 38 Found· C,67 87, 11 58

(3R)-3,6-Dimethylhepta-1,6-dien-3-ol **[(3R)-(–)-3]** The protected dienol **(3R)-12** (5 00, 23 6 mmol) was dissolved in dry methanol (70 ml) and K_2CO_3 (0 7 g) was added [36] The mixture was refluxed for 5 h and then the solvent was removed under reduced pressure The residue was taken with diethyl ether, washed with brine (3x50 ml) and dried (Na_2SO_4) The evaporation of the solvent at reduced pressure furnished an oil that was distilled to give pure **(3R)-3** (3.15g, 95%) bp 115-120°C/22mmHg (Kugelrohr air-bath temperature), $[\alpha]_D^{26}$ -15 66 (d 0 865), IR ν 3393, 2972, 2936 cm^{-1}, ^{1}H NMR δ 1 3 (3H, s), 1 55-1 80 (2H, m), 1 74 (3H, s), 1 89 (1H, s, exchanges with D_2O), 1 96-2 14 (2H, m), 4 6 (2H, bs), 5 00-5 31 (2H, m), 5 81-6 02 ppm (2H, m)

Anal Calcd for $C_9H_{16}O$ C,77 09, H,11 50 Found C,77 15, H,11 57

(3S)-3,6-Dimethylhepta-1,6-dien-3-ol **[(3S)-(+)-3]** The deprotection of (3S)-**12** was performed in a like manner to give **(3S)-3** (ee 64%, 95% yield) $[\alpha]_D^{26}$ +10 09 (d 0 865) IR and ^{1}H NMR spectra were identical with those of (3R)-**3**

Anal Calcd for $C_9H_{16}O$ C,77 09, H,11 50 Found C,77 18, H,11 35

(1S,2R,5S)-(+)-2,5-Dimethylbicyclo[3 2 0]heptan-endo-2-ol **[(1S,2R,5S)-(+)-2]** The photobicyclization reaction was performed according to the previously reported procedure [16] A solution of **(3R)-(–)-3** (10.0 g, 71.3 mmol) and copper(I)trifluromethanesulphonate-benzene complex (0 5 g) in anhydrous diethyl ether (600 ml) was irradiated 15 h with a 450-W Hanovia lamp in a quartz immersion well After completion of the irradiation (t l c control) the raction mixture was quenched with a mixture of crushed ice (100 g) and 30% NH_4OH (10 ml) The deep blue aqueous phase was separated and extracted with ether (2x50 ml) The combined organic extract were washed with brine and dried over $MgSO_4$ Removal of the solvent by rotary evaporation gave **(1S,2R,5S)-(+)-2** (9 54 g, 95%), mp 56-57°C from ethanol-water and successive sublimation at 65°C/15mmHg, $[\alpha]_D^{26}$ +26 40 (c 1 628, methanol) The spectroscopic data are identical with those above reported

Anal Calcd for $C_9H_{16}O$ C,77 09, H,11 50 Found C,77 16, H,11 40

(1R,2S,5R)-(–)-2,5-Dimethylbicyclo[3 2 0]heptan-endo-2-ol **[(1R,2S,5R)-(–)-2]** The photobicyclization reaction of **(3S)-(+)-3** gave **(1R,2S,5R)-(+)-2** in 95% yield· mp 56-57°C from ethanol-water

and successive sublimation at 65°C/15mmHg $[\alpha]_D^{26}$ -15 83 (c 1 610; methanol), ee 64% The spectroscopic data are identical with those above reported This sample of **(+)-2** was converted into pure **(1R,2S,5R,2'S)-5** by esterification with (2S)-(-)-NTP-Cl **[(–)-4]** and successive crystallization from *n*-hexane The reductive cleavage with $LiAlH_4$ according to the procedure previusly depicted, gave enantiomerically pure **(1R,2S,5R)-(–)-2** having $[\alpha]_D^{26}$ -26 87 (c 1 630, methanol)

Anal Calcd for $C_9H_{16}O$ C,77 09, H,11 50 Found C,77 21, H,11 43

Acknowledgements.

We thank the Consiglio Nazionale delle Ricerche - Italy, and Ministero dell'Università e della Ricerca Scientifica e Tecnologica - Italy, for financial support

REFERENCES AND NOTES.

1 Tumlinson, J H , Hardee, D D , Gueldner, R C , Thompson, A C , Hedin, P A , Minyard, J P *Science* **1969**, *166*, 1010

2 Francke, W - Convergency and Diversity in Multicomponent Insect Pheromones In "Advances in Invertebrate Reproduction - 4" Porchet, M , Audries, J -C and Dhainant, A Editors-Elsevier Science Publishers, **1986**, 327-336

3 Francke, W , Pan, M -L , Konig, W A , Mori, K , Puapoomchareon, P , Heuer, H , Vitè, J P *Naturwissenschaften* **1977**, *64*, 98

4 Francke, W , Bartels, J , Krohn, S , Schulz, S , Baader, E , Tengo, J , Schneider, D *Pure & Appl Chem* **1989**, *61*, 539

5 Booth, D C , Phillips, T W , Claesson, A , Silverstein, R M , Lanier, G N , Wesr, J R *J Chem Ecol* **1983**, *9*, 1

6 Hobbs, P D , Magnus, P D *J Am Chem Soc* **1976**, *98*, 4594

7 Seebach, D , Hungerbuhler, E - Syntheses of Enantiomerically Pure Compounds (EPC-Syntheses) - In "Modern Synthetic Methods" Scheffold, R Ed , Springer-Verlag, Berlin, **1980**, 91

8 Mori, K *Tetrahedron* **1978**, *34*, 915

9 Mori, K , Tamada, S *Naturwissenschaften* **1978**, *65*, 653

10 Jones, J B , Finch, M A W , Jakovac, I J *Can J Chem* **1982**, *62*, 2007

11 Meyers, A I , Fleming, S A *J Am Chem Soc* **1986**, *108*, 306

12 Webster, F X , Silverstein, R M *J Org Chem* **1986**, *51*, 5227

13 Demuth, M , Palomer, A , Sluma, H -D , Dey, A K , Kruger, C , Tsay, Y -H *Agew Chem* **1986**, *98*, 1093, *Angew Chem Int Ed Engl* **1986**, *25*, 1117

14 Mori, K , Miyake, M *Tetrahedron* **1987**, *43*, 2229

15 For a general review on synthesis of optically active pheromones, see Mori, K *Tetrahedron Report No 252*, *Tetrahedron* **1989**, *45*, 3233

16 Rosini, G , Marotta, E , Petrini, M , Ballini, R. *Tetrahedron*, **1985**, *41*, 4633

17 This unsaturated ketone was conveniently prepared from methallyl chloride and ethyl acetoacetate[16] and is now commercially available from Aldrich

18 (a) Salomon, R G , Ghosh, D J *Org Synth* **1984**, *62*, 125, (b) Salomon, R G , Coughlin, D J , Ghosh, S , Zagorski, M G *J Am Chem Soc* **1982** , *104*, 998

19 Rosini, G , Carloni, P , Iapalucci, M C , Marotta, E *Tetrahedron Asymmetry* **1990**, *1*, 751

20 Gerlach, H *Helv Chim Acta* **1968**, *51*, 1587

21 (2S)-Proline, (2S)-(–)-pyrrolidine-2-carboxylic acid is a naturally occurring proteogenic - amino acid and can be also prepared by fermentation (2R)-Proline, the (2R)-(+)-isomer, is significantly more costly, however, its synthetic availability from D-glutammic acid provides an affordable alternative Enders, D, Eichenauer, H , Pieter, R *Chem Ber* **1979**, *112*, 3703

22 Busson, R , Vanderhaege, H *J Org Chem* **1978**, *43*, 4438

23 Clark, C R , Barksdale, J M *Anal Chem* **1984**, *56*, 958

24 Bowden, K , Heilbron, I M , Jones, E R H , Weedon, B C L *J Chem Soc* **1946**, 39

25 Carlsen, P H J , Katsuki, T , Martin, V S , Sharpless, K B *J Org Chem* **1981**, *55*, 589

26 For an authoritative presentation and illustration of this strategy Hanessian, S - Total Synthesis of Natural Products The "Chiron" Approach - Pergamon Press, Oxford, **1983**

27 Ruzicka, L , Fornazir, V *Helv Chim Acta*, **1919**, *2*, 182

28 Bauer, K , Garbe, D Common Fragrance and Flavor Materials Preparation, Properties and Uses - VCH Verlagsgesellschaft mbH, Weinheim, **1985**

29 Ohloff, G , Klein, E , Schade, G US 3,240,821 (**1966**)

30 Cooke, F , Magnus, P *Organomethallics* **1982**, *1*, 897

31 Chemical purity was checked by comparison of proton and ^{13}C NMR spectra with those of authentic samples of linalool, enantiomeric purity was determined by using a chiral shift reagent, Eu(hfc)3 Wilson, W K , Scallen, T J , Morrow, C J J *Lipid Res* **1982**, *23*, 645

32 The last part of our synthetic scheme for racemic grandisol[16] has yet been verified to be available for the synthesis of enantiomeric pure (+)-grandisol [13]

33 Still, W C , Kahn, M , Mitra, A *J Org Chem 1978*, *43*, 2923

34 Griffith, W P , Ley, S V , Whitcombe, G P , White, A D *J C S Chem Commun* **1987**, 1625
For a review, see Griffith, W P , Ley, S V *Aldrichim Acta* **1990**, *23*, 13

35 Greenwald, R , Chaykovsky, M , Corey, E J *J Org Chem* **1963**, *28*, 1128

36 Hurst, D T , Mc Innes, A G *Can J Chem* **1965**, *43*, 2004