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Asymmetric Synthesis of Highly Enantiomerically Enriched (S)(-)-β-Bisabolene

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ASYMMETRIC SYNTHESIS OF HIGHLY ENANTIOMERICALLY ENRICHED (*S*)(-)- β-BISABOLENE[1]

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Abstract: (*S*)-β-Bisabolene, (*S*)-**1**, was synthetized by a synthetic route in which (*S*)-4-methyl-3-cyclohexene carboxylic acid, (*S*)-**10**, which was the key intermediate, was prepared *via* a highly diastereoselective $TiCl_4$-catalyzed Diels-Alder reaction between isoprene and the acrylate of commercial (*R*)-pantolactone, followed by hydrolysis. Compound (*S*)-**10** was then converted into ketone (*S*)-**13** using two different procedures. The best one of these, as regards the degree of stereospecificity, involved the reaction of (*S*)-**10** with 2 equiv of 4-methyl-3-penten-1-yllithium, **14**, in the presence of $CeCl_3$, and gave (*S*)-**13** having *ca.* 84 % ee. The Zr-promoted methylenation of this ketone afforded highly enantiomerically enriched (*S*)-**1**.

Both enantiomers of β-bisabolene, **1**, are known to occur naturally. In fact, (*R*)(+)-**1** is present in the essential oil of *Pinus sibirica*[2] and in the leaf oil of *Chamaecyparis nootkatensis*[3] and is also a component of the defensive secretion of soldiers of the North American termite, *Amithermes wheeleri*[4]. On the other hand,

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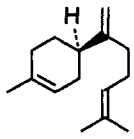
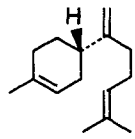
compound (*S*)(-)-**1** is probably the most widely occurring member of the bisabolane family in essential oils[5].

It has been also reported that compound **1**, having undefined stereochemistry, is present in the stems of the foliage of the Chinese date, *Zizyphus jujuba* (Rhamnaceae) and is biologically active towards *Reticulitermes lucifugus*[6], a termite of the fairly advanced family Rhinotermitidae, which establishes itself in the wood-structures of houses and monuments, in musea and libreries where it causes irreparable damage. In particular, it has been found that this sesquiterpene attracts *R. lucifugus* at 10^{-9} - 10^{-8} g/L, is inactive at 10^{-7} g/L and strongly repells this termite at 10^{-6} - 10^{-5} g/L[6].

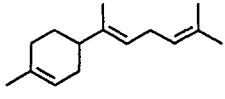


(*R*)(+)-**1**

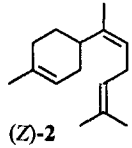


(*S*)(-)-**1**

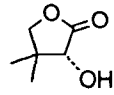
In the course of a current investigation aimed to develop a method suitable for monitoring and/or controlling *R. lucifugus,* which is based on the use of synthetic conspecific trail-following pheromone components[7] and/or their structural analogues[7] or naturally-occurring trail attractants[8], recently we developed new, selective and efficient syntheses of racemic **1** as well as of racemic (*E*)-α- and (*Z*)-α-bisabolene[8], (*E*)-**2** and (*Z*)-**2**, which are also present in the stems of *Z. jujuba* and are possible trail-attractants of *R. lucifugus*[6,8].



(*E*)-**2**



(*Z*)-**2**

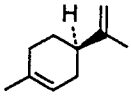


(*R*)-**3**

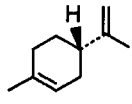
Since we were also interested to evaluate the relationship between absolute configuration and bioactivity of compound **1**, more recently we began a study on the synthesis of both enantiomers of this substance. We now wish to report the results obtained in an investigation on an asymmetric synthesis of highly enantiomerically enriched (*S*)(-)-**1**, in which (*R*)-pantolactone, (*R*)-**3**, an inexpensive commercially

available compound derived from the chiral pool of natural products, has been used as a chiral auxiliary.

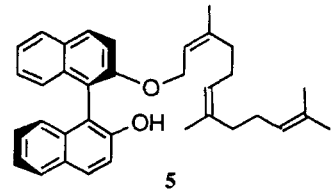
It must be noted that our approach is quite different from those previously employed for the synthesis of optically active β-bisabolene[9]. In fact, three of the four syntheses reported so far in the literature for optically active **1**[9a-c] were based on the use of (*R*)- or (*S*)-limonene, (*R*)- and (*S*)-**4**, respectively, as chiral building block. On the other hand, the fourth synthesis of (*S*)-**1** involved the enantioselective cyclization of (*R*)(+)-binaphtol (*Z,Z*)-monofarnesyl ether, **5**, in the presence of (2,4,6-tri-*tert*-butylphenoxy)isobutylaluminum trifluoromethane-sulphonate[9d]. However, such reaction afforded a mixture of bisabolenes from which (*S*)-**1** was separated by TLC on $AgNO_3$ impregnated silica gel[9d].



(*R*)-**4**



(*S*)-**4**



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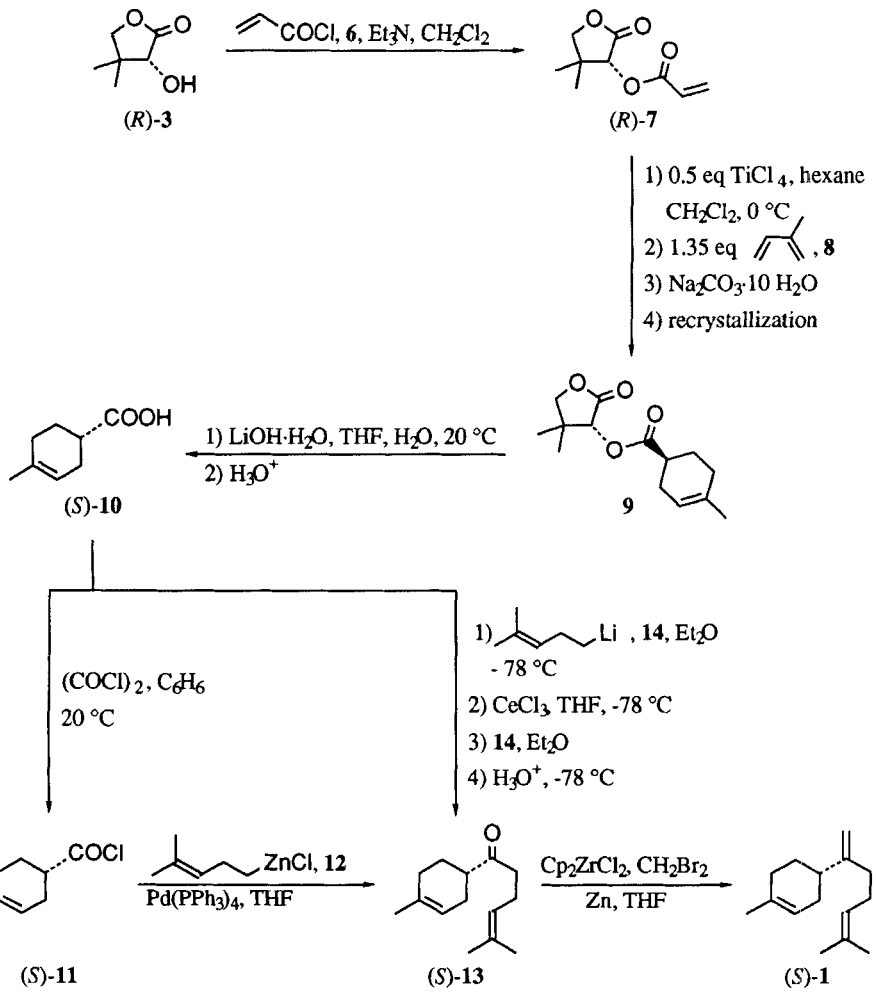
The reaction sequence used for the preparation of (*S*)-**1** starting from (*R*)-**3** is depicted in Scheme 1. In this sequence, 94.7 % optically pure (*S*)-4-methyl-3-cyclohexene carboxylic acid, (*S*)-**10**, represented the key intermediate. Such carboxylic acid was prepared *via* a highly diastereoselective $TiCl_4$-catalyzed Diels-Alder reaction between (*R*)-2-propenoyloxy-3,3-dimethyl-γ-butyrolactone, (*R*)-**7**, and isoprene, **8**, followed by saponification[10]. In particular, compound (*R*)-**7**, which was prepared in 82 % yield from (*R*)-**3** and propenoyl chloride, **6**[10], was dissolved *in* CH_2Cl_2/hexane and sequentially treated at 0 °C under stirring with 0.5 equiv of a 1 M hexane solution of $TiCl_4$ and 1.35 equiv of **8**[10]. After stirring at 0 °C for 3 h, the reaction mixture was treated with a molar excess of $Na_2CO_3 \cdot 10H_2O$ and filtered. Evaporation of the filtrate followed by purification of the so obtained residue by MPLC on silica gel and four recrystallizations from cold hexane allowed to obtain in 70 % yield compound **9** having diastereoisomeric purity higher than 99.9 %. Finally, treatment of a solution of **9** in THF and water with $LiOH \cdot H_2O$ for 24 h at room temperature followed by extraction with Et_2O and acidification of the

Scheme 1



resultant aqueous phase allowed to obtain 94.7 % optically pure (*S*)-**10**, $[\alpha]^{20}_{D}$ -101.4 (c 4.07, 95 % EtOH), in quantitative yield. Interestingly, by concentration of the organic extract obtained from the saponification of **9** it was possible to recover quantitatively the chiral auxiliary (*R*)-**3**.

Then, it was attempted to convert compound (*S*)-**10** into highly enantiomerically enriched (*S*)-**1** by a reaction sequence identical to that previously reported for the synthesis of racemic **1** starting from (*R*)(*S*)-**10**[8]. Thus, (*S*)-**10** was reacted with oxalyl chloride in dry benzene at room temperature to give crude (*S*)-**11**. This compound was then treated with 4-methyl-3-penten-1-ylzinc chloride, **12**[8], in THF, in the presence of a catalytic amount of $Pd(PPh_3)_4$, to give (*S*)-2-methyl-6-keto-6-(4-methyl-3-cyclohexen-1-yl)-2-hexene, (*S*)-**13**, $[\alpha]^{25}_D$ - 53.4 (c 10.48, hexane), in 63 % yield based on (*S*)-**10**.

Before converting (*S*)-**13** into (*S*)-**1** some attempts were made to evaluate the enantiomeric excess of this ketone by HPLC analysis on columns containing chiral stationary phases. The best result was obtained using a Chiralgel OJ column, although the peaks of the enantiomers of **13** were not completely separated to the baseline from each other[16]. Using this column it was possible to establish that compound (*S*)-**13** had *ca.* 70 % ee. This unsatisfactory value could indicate that a significant racemization, which, at least in part, could be attributed to the step involving the preparation of (*S*)-**11**, had occurred in the conversion of (*S*)-**10** into (*S*)-**13**.

Compound (*S*)-**13** was then treated with 8.2 equiv of granular zinc metal, 1.2 equiv of Cp_2ZrCl_2 and 2.3 equiv of CH_2Br_2 in THF to give compound (*S*)-**1**, $[\alpha]^{30}_D$ - 51.2 (c 0.33, 96 % EtOH), in 90 % yield.

A comparison between the value of the specific rotatory power of (*S*)-**1** so prepared and those reported in the literature for both enantiomers of this sesquiterpene (Table) allowed to confirm that our sample of (*S*)-**1** had ee ≤ 70 %.

Finally, in the hope to obtain (*S*)-**1** starting from (*S*)-**10** without any significant racemization, we prepared such sesquiterpene by a different route. In particular, according to a recent procedure for the direct conversion of carboxylic acids into ketones[17], a solution of the lithium salt of (*S*)-**10**, which was obtained by reaction of a THF solution of (*S*)-**10** with 1 equiv of a 0.57 M Et_2O solution of 4-methyl-3-penten-1-yllithium, **14**, at -78 °C, was treated at -78 °C with a THF suspension of 2 equiv of $CeCl_3$ followed by addition of 1 equiv of a 0.57 M Et_2O solution of **14**. The resulting mixture was stirred for 23 h at -78 °C and then quenched at -78 °C by

Table

Values reported in the literature for the rotatory power of (*S*)- and (*R*)-β-bisabolene, (*S*)- and (*R*)-**1**

Compound (*S*)-1		Compound (*R*)-1	
Rotatory power	Ref.	Rotatory power	Ref.
α^{15} - 67	11	α_D + 47.2	9b
α_D - 66.80	12	$[\alpha]^{20}_D$ + 56 (c 2.94, EtOH)	9d
$[\alpha]^{30}_D$ - 68.0 (c 0.33, EtOH)	5	$[\alpha]^{21}_D$ + 41 ± 3 (c 0.22, CCl_4)	4
$[\alpha]^{20}_D$ - 84.4	13	$[\alpha]^{23}_D$ + 101 ± 11 (c 21.5, hexanes)	15
$[\alpha]_D$ - 62.92	14	$[\alpha]^{20}_D$ + 75	2
		$[\alpha]_D$ + 52 ± 20	3
		$[\alpha]^{30}_D$ + 74 (c 0.36, EtOH)	5

addition of 5 % HCl. The crude reaction product was purified by MPLC on silica gel to give compound (*S*)-**13**, $[\alpha]^{25}_D$ - 70.2 (c 10.46, hexane), in 47 % yield. HPLC analysis on Chiralgel OJ column showed that this ketone had *ca.* 84 % ee. Thus, this procedure for preparing (*S*)-**14** involved also a partial racemization (*ca.* 6 %), which, however, was smaller than that encountered in the route in which compound (*S*)-**11** was an intermediate.

Methylenation of this sample of (*S*)-**13** according to the procedure described above afforded compound (*S*)-**1**, $[\alpha]^{30}_D$ - 65.6 (c 0.34, EtOH), in 90 % yield.

Several attempts to evaluate the enantiomeric purity of this sesquiterpene either by NMR analysis in the presence of α-cyclodextrin, chiral shift reagents or chiral solvents[18] or by GLC on columns containing α- or β-cyclodextrins as chiral stationary phases were unsuccessful[19]. Therefore, we cannot know if the methylenation of (*S*)-**13** involves a partial racemization. However, even if it is impossible to assign a well defined value to the enantiomeric purity to the samples of (*S*)-**1** prepared in this work, we could attribute a *ca.* 88 % optical purity to (*S*)-**1**

having $[\alpha]^{30}_{D}$ - 65.6 (EtOH), if, according to what recently reported in the literature[9d], we assume $[\alpha]^{30}_{Dmax}$ 74 (EtOH) for enantiomerically pure **1**[5]. This value of the optical purity should not be much different from the ee evaluated for (*S*)-**13** used as precursor to this compound.

EXPERIMENTAL

GLC analyses were performed on a Dani 6500 gas-chromatograph with a PTV injector and equipped with a Dani data station 86.01. Two types of capillary columns were used: a SE-30 bonded FSOT column (30 m × 0.25 mm i.d.) and a AT-Wax bonded FSOT column (30 m × 0.25 mm i.d.). TLC analyses were performed using plastic sheets Merck silica gel 60 F_{254} . Purifications by MPLC were performed on a Büchi 681 instrument, using a Bischoff 8100 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin-Elmer 8500 gas-chromatograph. ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz using TMS as an internal standard. Measuremments of optical acivity were performed using a Perkin-Elmer 142 spectropolarimeter and 1 dm tubes. HPLC analyses were performed using a Twincle (Jasco) chromatograph. The enantiomeric excess (ee) of compound (*S*)-**13** was evaluated by HPLC on a Chiralgel OJ column (250 mm x 4 mm i.d.) [eluant: hexane/*i*-PrOH = 9 : 1; λ = 280 nm; flow = 0.5 ml/min].

All reactions of air and water sensitive materials were performed in flame dried glassware under an atmosphere of argon. Air and water sensitive solutions were transferred with hypodermic syringes or double-ended needles.

The following compounds were prepared according to the literature: $Pd(PPh_3)_4$[20], 1-bromo-4-methyl-3-pentene[7].

*(R)-2-Propenoyloxy-3,3-dimethyl-γ-butyrolactone, (R)-***7**

According to the literature[10], propenoyl chloride, **6** (43.5 g, 480 mmol) was added over 1 h to a stirred solution of (*R*)-pantolactone, (*R*)-**3**, $[\alpha]^{25}_{D}$ - 49.8 (c 2, H_2O) (50.00 g, 384.2 mmol) and Et_3N (58.30 g, 576.2 mmol) in dry CH_2Cl_2 (480 ml),

which was stirred at -24 °C under nitrogen. The resulting mixture was stirred at -24 °C for 4.5 h and then sequentially washed with a large excess of aqueous 1 N HCl, a saturated $NaHCO_3$ solution and water. The organic phase was dried, concentrated under reduced pressure and the residue was distilled to give chemically pure compound (*R*)-**7** (57.88 g, 82 % yield): b.p. 79 °C/0.03 Torr; $[\alpha]^{20}_D$ + 6.56 (c 17.2, CH_2Cl_2); ^1H NMR ($CDCl_3$), *δ*: 6.54 (1H, dd, *J* = 17.2 and 1.4 Hz, (*E*)-H-3'), 6.23 (1H, dd, *J* = 17.2 and 10.3 Hz, H-2'), 5.98 (1H, dd, *J* = 10.3 and 1.4 Hz, (*Z*)-H-3'), 5.45 (1H, s, H-2), 4.07 (2H, s, H-4), 1.23 (3H, s, CH_3), 1.14 ppm (3H, s, CH_3). Lit[10] $[\alpha]^{20}_D$ + 6.5 (c 17, CH_2Cl_2); b.p. 84 °C/0.1 Torr.

GLC analysis showed that compound (*R*)-**7** had chemical purity higher than 99.5 %.

(R)-2-[(S)-4-Methyl-3-cyclohexene-1-carboxy]-3,3-dimethyl-γ-butyrolactone, 9

A 1 M hexane solution of $TiCl_4$ (51.6 ml, 51.6 mmol) was added under nitrogen to a stirred solution of (*R*)-**7** (19.00 g, 103.2 mmol) in dry CH_2Cl_2 (100 ml) which was maintained at 0 °C. After stirring for 45 min, isoprene, **8** (9.47 g, 139 mmol) was added and the resulting mixture was stirred at 0 °C for 3 h. After this period GLC analysis of a sample of the reaction mixture, which was quenched with finely pulverized $Na_2CO_3 \cdot 10H_2O$ and extracted with CH_2Cl_2, showed the absence of (*R*)-**7** and the presence of a new compound. Thus, the reaction mixture was quenched by addition of $Na_2CO_3 \cdot 10H_2O$ (59.32 g, 207.3 mmol) and filtered on Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel using a mixture of hexane and ethyl acetate (85 : 15 *v*/*v*) as eluant. GLC analysis of the collected chromatographic fractions which contained the desired compound showed that **9** was contaminated by *ca.* 7 % of the corresponding (*R,R*)-diastereoisomer. Four recrystallizations of this product from cold hexane allowed to obtain 99.9 % diastereoisomerically pure **9** (18.13 g, 70 % yield): m.p. 52 °C. ^1H NMR ($CDCl_3$), *δ*: 5.42 - 5.32 (2H, m, H-3 and H-2'), 4.04 (2H, s, H-4'), 2.76 - 2.58 (1H, m, H-1), 2.36 - 2.21 (2H, m, H-2), 2.13 - 1.71 (4H, br m, H-5 and H-6), 1.66 (3H, br s, CH_3 at C-4), 1.20 (3H, s, CH_3 at C-3'), 1.11 ppm (3H, s, CH_3 at C-3'). MS (*m*/*z*) (%): 252 (2), 123 (3), 122 (7), 113 (4), 99 (9), 95 (29), 94 (100), 93 (16), 79 (22). Lit[10] m.p. 56 °C.

(S)-4-Methyl-3-cyclohexene carboxylic acid, (S)-10

A solution of compound **9** (15.87 g, 62.90 mmol) in THF (176 ml) was slowly addded to a solution of $LiOH \cdot H_2O$ (11.17 g, 266.2 mmol) in water (141 ml) and the resulting mixture was vigorously stirred at room temperature for 24 h. THF was then evaporated under reduced pressure and the resulting aqueous solution was extracted with Et_2O. Concentration of the Et_2O extract allowed to obtain pure (*R*)-**3** (8.1 g, 99 % yield). The resulting aqueous phase was acidified at 0 °C with 15 % H_2SO_4, extracted repeatedly with a mixture of pentane and CH_2Cl_2 (98 : 2 *v/v*), dried and concentrated *in vacuo* to give (*S*)-**10** (8.82 g, 100 % yield). GLC analysis showed that this compound had chemical purity higher than 99.5 %. Compound (*S*)-**10**, which was recrystallized at 5 °C from hexane, had: m.p. 98-98.5 °C; $[\alpha]^{20}_D$ - 101.4 (c 4.07, 95 % EtOH). Lit[10] $[\alpha]^{20}_D$ - 107 (c 4, 95 % EtOH). Compound (*R*)(*S*)-**10** had: m.p. 99 °C[21].

(S)-4-Methyl-3-cyclohexene-1-carbonyl chloride, (S)-11

Oxalyl chloride (4.3 ml, 49.4 mmol) was added dropwise to a stirred solution of compound (*S*)-**10** (3.0 g, 21.4 mmol) in dry benzene (29 ml) and the resulting mixture was stirred for 4.5 h at room temperature. After this period, a GLC analysis showed that the reaction was almost complete. Thus the reaction mixture was concentrated at room temperature under reduced pressure (45 Torr). Crude compound (*S*)-**11** so obtained was used in the next step without any further purification.

(S)-2-Methyl-6-keto-6-(4-methyl-3-cyclohexen-1-yl)-2-hexene, (S)-13

First procedure: A solution of 1-bromo-4-methyl-3-pentene[7] (3.66 g, 22.5 mmol) in dry THF (19 ml) was added dropwise to a stirred mixture of Mg (0.84 g, 34.5 mmol) and dry THF (7 ml) maintained under reflux. After completion of the addition, the mixture was refluxed for additional 1 h, cooled to room temperature and allowed to settle. The clear solution so obtained was transferred into a slurry of dry $ZnCl_2$ (3.07 g, 22.5 mmol) in THF (11 ml) cooled to 0 °C. The resulting mixture was stirred at room temperature for 20 min and then cooled to 0 °C. $Pd(PPh_3)_4$ (1.06 g, 0.92 mmol) and a solution of crude compound (*S*)-**11** (21.4 mmol) in dry THF (10

ml) were sequentially added. The resulting mixture was stirred for 15 h at 0 °C, then poured into a large excess of cold diluted HCl and extracted repeatedly with Et_2O. The combined organic extracts were washed with diluted HCl, water, an aqueous $NaHCO_3$ solution and water, dried and filtered on Celite. The filtrate was concentrated *in vacuo* and the residue was diluted with hexane and filtered on Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (98.5 : 1.5 *v*/*v*) as eluant, to give compound (*S*)-**13** (2.80 g, 63 % yield based on (*S*)-**10**): $[\alpha]^{25}_D$ - 53.4 (c 10.48, hexane). ^1H NMR ($CDCl_3$), δ: 5.44 - 5.34 (1H, m, H-3'), 5.06 (1H, *t pseudo*-hept, *J* = 7.1 and 1.4 Hz, H-3), 2.60 - 2.43 (1H, m, H-1'), 2.49 (2H, t, *J* = 7.1 Hz, H-5), 2.24 (2H, *pseudo*-q, *J* = 7.1 Hz, H-4), 2.19 - 1.85 (5H, br m, H-2', H-5', H-6'ax or H-6'eq), 1.68 - 1.61 (6H, m, (*Z*)-H-1 and (*E*)-H-1), 1.65 - 1.49 (1H, m, H-6'eq or H-6'ax), 1.61 ppm (3H, s, CH_3 at C-4'). The spectral properties of this compound were in good agreement with those previously reported for racemic **13**[8]. HPLC analysis on a Chiralgel OJ column showed that (*S*)-**13** had ca. 70 % ee.

Second procedure: A 0.57 M Et_2O solution of 4-methyl-3-penten-1-yllithium, **14** (35.6 ml, 20.3 mmol), which was prepared by reaction between an Et_2O solution of 1-bromo-4-methyl-3-pentene and a molar excess of lithium sand containing 1 % of sodium at -15 °C, was added dropwise to a stirred solution of compound (*S*)-**10** (2.84 g, 20.3 mmol) in dry THF (100 ml) maintained at -78 °C and the resulting mixture was stirred for 20 min at -78 °C. A suspension of $CeCl_3$ (10.00 g, 40.57 mmol) in dry THF (80 ml) cooled to -78 °C was cannulated to the lithium carboxylate solution and the resulting mixture was stirred for 35 min at -78 °C. After this period, a 0.57 M Et_2O solution of **14** (20.3 mmol) was added dropwise and the mixture was stirred for 23 h at -78 °C. Finally, 5 % aqueous HCl (60 ml) was added and the mixture was allowed to warm up to room temperature. It was then repeatedly extracted with Et_2O and the collected organic extracts were washed with a 5 % aqueous $NaHCO_3$ solution and water until neutrality, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (98.5 : 1.5 *v*/*v*) as eluant, to give compound (*S*)-**13** (1.95 g, 47 % yield): $[\alpha]^{25}_D$ - 70.2 (c 10.46, hexane). GLC analysis showed that this compound had 99.8 % chemical purity. On

the other hand, HPLC analysis on a Chiralgel OJ column showed that (*S*)-**13** had *ca.* 84 % enantiomeric purity. The spectral properties of this compound were in good agreement with those of (*S*)-**13** prepared according to the first procedure.

(S)-β-Bisabolene, (S)-1

Granular zinc metal (4.27 g, 65.3 mmol), which was previously washed with 5 % aqueous HCl, water, acetone and Et_2O and dried *in vacuo*, zirconocene dichloride (2.86 g, 9.78 mmol), dry THF (25 ml), compound (*S*)-**13** having $[\alpha]^{25}_D$ - 53.4 (c 10.48, hexane) (1.64 g, 7.95 mmol) and dry CH_2Br_2 (3.12 g, 18.0 mmol) were sequentially added in a dry argon flushed flask. The mixture was stirred at room temperature for 17 h before being quenched at 0 °C with ice-water. It was then poured into a large excess of ice-water and filtered. The filtrate was repeatedly extracted with pentane and the combined organic extracts were washed with water, dried, filtered on Celite and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, using hexane as eluant, to give 99 % chemically pure (*S*)-**1** (1.47 g, 90 % yield): $[\alpha]^{30}_D$ - 51.2 (c 0.328, 96 % EtOH). The spectral properties of this compound were in very good agreement with those previously reported for racemic **1**[8].

When this same procedure was employed for the methylenation of (*S*)-**13** having $[\alpha]^{25}_D$ - 70.2 (c 10.46, hexane), compound (*S*)-**1** having $[\alpha]^{30}_D$ - 65.6 (c 0.336, EtOH) or $[\alpha]^{30}_D$ - 65.2 (c 0.330, 96 % EtOH) was obtained in 90 % yield.

REFERENCES AND NOTES

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16. We thank Prof. Carlo Rosini for the measurements of the enantiomeric excess of compound (*S*)-**13** by HPLC analysis on a Chiralgel OJ column.

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18. The ^{1}H NMR spectra were registered using a Varian VXR 300 Mz and a Bruker AMX 600 MHz spectrometer.

19. Only when a column containing permethylated β-cyclodextrin was used as a GLC chiral stationary phase (25 m x 0.33 mm i.d.), a small separation of the peaks attributable to the two enantiomers of **1** was observed. Nevertheless, such separation was insufficient for a quantitative determination of the enantiomeric purity of (*S*)-**1**.

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