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The Asymmetric Diels-Alder Cycloaddition Using Ethyl (−)-(*Z*)-(*R*)$_S$-2-Methyl-3-(*p*-tolylsulfinyl)propenoate: Application to an Enantioselective Synthesis of (+)-*epi*-β-Santalene

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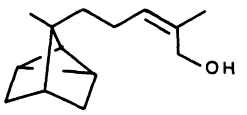
The Diels-Alder reaction of ethyl (−)-(*Z*)-(*R*)$_S$-2-methyl-3-(*p*-tolylsulfinyl)propenoate (**6**)[1] with cyclopentadiene gave the cycloadducts **7**, **8**, and **9** in a high diastereoselective manner. The cycloadduct **7** was transformed into the acetal (−)-**25**. The racemic **25** was used as an intermediate in the synthesis of (±)-β-santalol. Thus, the chiral acetal (−)-**25** should provide a route to (−)-β-santalol. The cycloadduct **8** was converted into (+)-*epi*-β-santalene in 11 steps.

East Indian sandalwood oil was obtained from the tree, *Santalum album* L., growing in the forest of Mysore, India.[2] The oil is prized for its woody sweet and very long-lasting odor. Recently, it was pointed[3] that the orfactory character was responsible mainly for two major components of the essential oil, (+)-α-santalol (**1**), and (−)-β-santalol (**2**). Of course, many of the minor components, e.g., (−)-β-santalene (**3**), (+)-*epi*-β-santalene (**4**), and (+)-*epi*-β-santalol (**5**) are also considered to contribute the perfume character. The structural relationship and absolute configuration of these sesquiterpenes were established by Money and co-workers.[4] Since the appearence of the pioneering work of Corey,[5] Brieger,[6] and Money,[7] a number of



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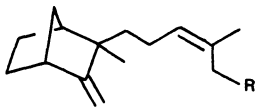
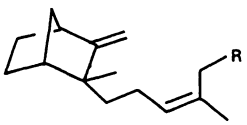


2 R = OH
3 R = H

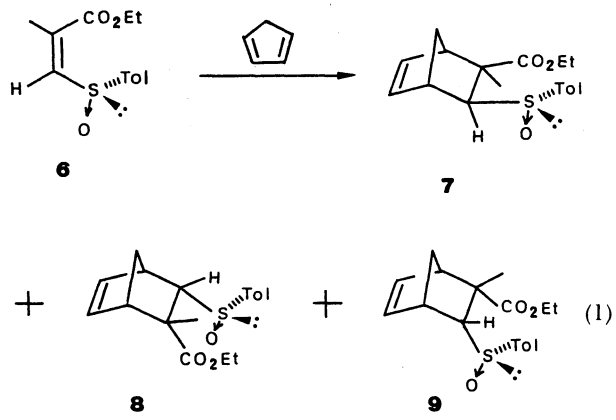


4 R = H
5 R = OH

syntheses of the santalols and santalenes have come on the scene.[8] However, there have been only two reports on the chiral synthesis of these sesquiterpenes: an elegant synthesis of (−)-**3** by Oppolzer[9] and a novel synthesis of some sesquiterpenes by Money.[4] Especially, the Oppolzer's synthesis involved an asymmetric Diels-Alder cycloaddition as a crucial step.

In the past few years, an asymmetric Diels-Alder reaction employing α,β-unsaturated sulfoxides has received a great deal of attention.[10] Because of the high diastereodifferentiation, the interpretation of the stereochemical course of the cycloadditions has been recently reported by Hehre from theoretical interest.[11] However, there have been few reports on the application to natural product synthesis, based upon the strategy of the asymmetric cycloaddition using chiral sulfoxides.[12]

As part of our investigation in this area, we reported that the Diels-Alder cycloaddition of the sulfoxides **6** and cyclopentadiene gave the cycloadducts **7**, **8**, and **9**



6 **7** **8** **9** (1)

(ratio 32:66:2) in 92% combined yield. The diastereomeric excesses of the exo and endo adducts were proved to be 100 and 94% by HPLC analysis, respectively.[13] The absolute configuration of **7** was determined by chemical correlation. Although the absolute stereochemistry of the endo diastereomers was not clarified, we pointed out that the structure of **8** should be shown as depicted in Eq. 1, based upon our proposal of the steric course in the cycloaddition.

Since chirons[14] **7**—**9** derived from **6** possess functionalized bicyclo[2.2.1]heptane systems, the bicyclic sesquiterpenes such as **2** and **4** seemed to be attractive as a synthetic target molecule. In a preliminary communication,[15] we have described the use of the chirons **7** and **8** for the chiral synthesis of the bicyclic sesquiterpenes. In this paper we report in details these results.

Results and Discussion

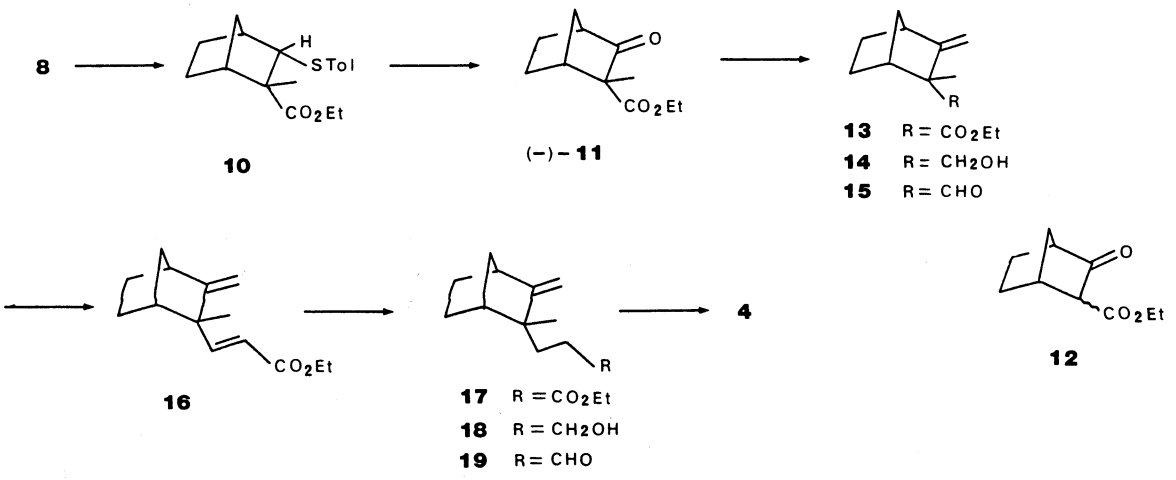
Synthesis of (+)-*epi*-β-Santalene. At the outset, we undertook the transformation of the sulfinyl group in

8 into the carbonyl function (Scheme 1). Hydrogenation of **8** ($[\alpha]_D^{19}$ −4.8°) over Pd on carbon followed by reduction of the sulfinyl group gave the sulfide **10** ($[\alpha]_D^{26}$ −7.32°) in 92% yield. Transformation of **10** into the keto ester (−)-**11** ($[\alpha]_D^{26}$ −7.15°) proceeded smoothly by chlorination with *N*-chlorosuccinimide (NCS) and subsequent oxidative hydrolysis,[16] in 85% yield. The stereostructure of (−)-**11** was ascertained by the following experiment. (±)-Norcamphor was ethoxycarbonylated with ethyl cyanoformate[17] under kinetically controlled conditions affording ester (±)-**12** whose enolate was stereoselectively methylated on the less hindered exo face of the ester to give (±)-**11**. The spectral and gas chromatographic characteristics were identical with those of (−)-**11** derived from **8**. The enantiomeric excess of (−)-**11** was proved to be no less than 97% by ^{1}H NMR examination in the presence of Eu(hfc)$_3$.

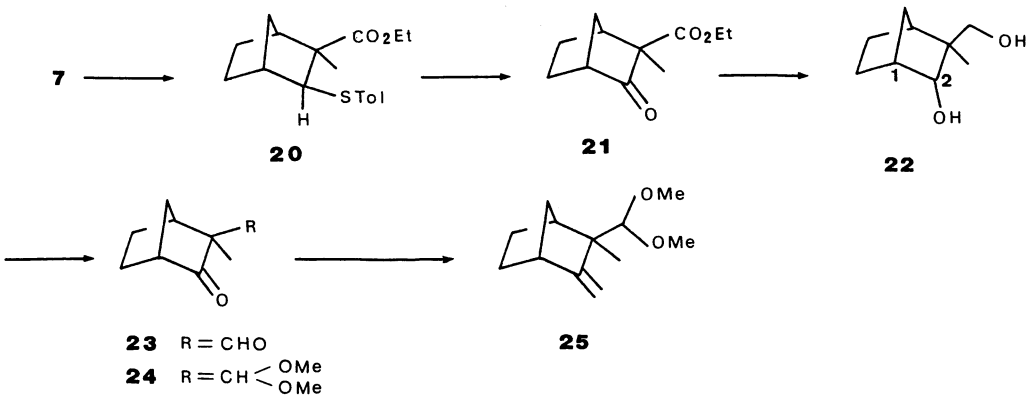
The next stage was set for the introduction of the terminal olefin in (−)-**11**. Reaction of (−)-**11** with a Wittig type reagent (methylenetriphenylphosphorane or the carbanion generated from diethyl methylphosphonate) did not produce the desired product **13**. In order to introduce the terminal olefin at a later stage, we tried to protect the keto group in (−)-**11**. Several attempts under a variety of conditions were unsuccessful, probably due to the steric hindrance. Finally, methylenation of the hindered carbonyl in (−)-**11** was best carried out by the Nozaki's method[18] (CH_2Br_2/Zn/$TiCl_4$) to produce **13** ($[\alpha]_D^{29}$ −46.3°) in 40% yield.[19]

The procedure adopted for converting the ester group in **13** into the requisite 4-methyl-3-pentenyl side chain is as follows. Reduction of **13** with diisobutylaluminium hydride (DIBAL, 2 equiv) gave the alcohol **14** ($[\alpha]_D^{26}$ + 96.2°) in quantitative yield. Pyridinium chlorochromate (PCC) oxidation[20] of **14** yielded the unstable aldehyde **15** (90%), $[\alpha]_D^{18}$ +17.1°, which was subjected to the Emmons-Horner condensation (triethyl phosphonoacetate, *n*-BuLi) giving the unsaturated ester **16** (96%), $[\alpha]_D^{26}$ −136°, as a single *E*-isomer. Reaction of **16** with Li-NH_3 gave the alcohol **18** in low yields. Good yields of **18** were obtained by the following operations. Hydrosilylation of **16** with triethylsilane in the presence of Wilkinson catalyst ($(Ph_3P)_3RhCl$) followed by ethanolysis provided the ester **17**, $[\alpha]_D^{25}$ +25.8°, in quantitative yield.[21] The spectroscopic data were consistent with those reported previously by Christenson and Willis in their synthesis of racemic **4**,[8b] According to the procedure of Christenson,[22] **17** was converted into (+)-*epi*-β-santalene by a 3-step sequence in 51% overall yield; reduction (DIBAL), PCC oxidation, and Wittig reaction. The spectral data (NMR, IR) were identical with those of an authentic sample kindly supplied by Dr. P. Christenson and the optical rotation ($[\alpha]_D^{27}$ +26.4°) was in good agreement with that reported in the literature ($[\alpha]_D^{27}$ +26.9°).[4]

Synthesis of the Intermediate (−)-25 of (−)-β-Santalol. In a manner similar to the first step of the synthesis of (+)-**4** the exo sulfoxide **7** was converted into the keto ester **21**, $[\alpha]_D^{25}$ −93.7° (Scheme 2). The structure of **21** was confirmed by direct comparison with that independently obtained by ethoxycarbonylation of (±)-3-methylnorcamphor.[23] Because the methylenation of the hindered keto group in **21** had been proved to be difficult, we chose the transformation of the ester group. The ester **21** was reduced with lithium aluminium hydride (LAH) to give the diol **22** (63%), $[\alpha]_D^{25}$ −8.5°, as a single isomer. The coupling constant ($J_{1,2}$=4 Hz) of the NMR spectrum showed that the C-2 hydroxyl group was located in the endo configuration. Swern oxidation[24] of **22** afforded the unstable keto aldehyde **23** (96%), and the aldehydic group was then selectively acetalized[25] with trimethyl orthoformate in the presence of cerium trichloride giving the acetal (−)-**24** (72%), $[\alpha]_D^{24}$ −62.6°. The enantiomeric excess (ee) of (−)-**24** was proved to be >97% as judged by NMR spectroscopy using Eu(hfc)$_3$. The exocyclic methylene group was introduced by the Nozaki's method to give (−)-**25** , $[\alpha]_D^{24}$ −119°, in 30%



Scheme 1.



Scheme 2.

yield. Since the absolute configuration of a chiron **7** have been determined,[13] the absolute stereochemistry of (−)-**25** should be deduced as depicted in Scheme 2. Racemic **25** was employed as an intermediate in the synthesis of (±)-**2** by the BASF group.[26] Having chiral acetal (−)-**25** in hand, it will be possible to transform the intermediate into (−)-**2**.

In conclusion, the chiron **7** was converted into a key intermediate in the synthesis of (−)-β-santalol. The chiron **8** was transformed into (+)-*epi*-β-santalene in enantiomerically pure form. Therefore, the absolute stereochemistry of the cycloadduct **8** was proved to be depicted in this paper. Based on our proposal[13] in the cycloaddition of a chiral sulfoxide, it was found that absolute stereostructure of the adducts could be predictable. And, we believe that the chirons would serve as the chiral intermediates for the synthesis of other natural products by transformation of the functionality such as the olefin, sulfinyl group and ethoxycarbonyl groups.

Experimental

The melting points and boiling points are uncorrected. ^{1}H NMR spectra were determined on a JEOL PMX-60, a Varian XL-200 or a JEOL GX-270 spectrometer. IR spectra were recorded on a JASCO A-102. Mass determinations were obtained on a JEOL D-200 spectrometer. Optical rotations were taken with a JASCO DIP-140 digital polarimeter. Gas chromatography was carried out on a Shimadzu GC-4A instrument with a column packed with 10% SE-30.

All experiments were carried out under a slight positive pressure of argon. Column chromatography was performed with Nakarai Chemicals 70—230 mesh silica gel. Wako's precoated thin-layer silica $PF70_{254}$ plates were used for monitoring the reactions. MPLC (medium-pressure chromatography) was performed with a Michael-Miller column (Ace Glass Co.) packed with 230—400 mesh silica gel (Nakarai Chemicals). Analytical high performance liquid chromatography (HPLC) was carried out on a Waters Associates chromatograph by using a μ-Polasil column and monitoring at 254 nm. Peak areas were measured with a Shimadzu (Chromatopac C-R3A) integrator. Evaporation of the solvents was performed by a rotary evaporator below 15 °C.

Ethyl (−)-(*Z*)-(*R*)$_s$-2-Methyl-3-(*p*-tolylsufinyl)propenoate (6). To a stirred solution of diethyl *p*-tolylsulfinylmethylphosphonate[13] (4.74 g, 16.3 mmol), $[\alpha]_D^{24}$ +96.3° (*c* 1.3, $CHCl_3$) in dry THF (50 ml) was added dropwise 1.56 M (1 M=1 mol dm^{-3}) *n*-BuLi in hexane (21 ml, 32.8 mmol) at −80 °C over a period of 9 min. After stirring at the same temperature for 30 min freshly distilled ethyl pyruvate (3.5 ml, 31.9 mmol) in dry THF (20 ml) was added dropwise for 10 min. After an additional 10 min the orange-colored mixture was quenched with 3% hydrochloric acid to become slightly acidic. The solvent was removed by a rotary evaporator and the aqueous solution was extracted with $CHCl_3$ (3×100 ml). The extracts were washed with water (3×100 ml), dil. $NaHCO_3$ aq (2×100 ml), sat. brine (100 ml) and dried ($MgSO_4$). After evaporation of the solvent the crude oil was purified by MPLC (hexane-ethyl acetate 7:3). Initial fractions contained pure (*E*)-**6** (1.033 g, 25%). Late fractions gave pure (*Z*)-**6** (1.222 g, 33%). (*E*)-**6**: bp 125—130 °C/0.1 mmHg (1 mmHg=133.322 Pa); $[\alpha]_D^{25}$ −78.9° (*c* 1.26, $CHCl_3$); IR (neat) 1730, 1630, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.28 (t, *J*=7 Hz, 3H), 2.30 (d, *J*=2 Hz, 3H), 2.45 (s, 3H), 4.22 (q, *J*=7 Hz, 2H), 7.18 (m, 1H), 7.33, 7.58 (ABq, *J*=8 Hz, 2×2H). Found: C, 61.76; H, 6.24%. Calcd for $C_{13}H_{16}O_3S$: C, 61.87; H, 6.40%; MS *m/z* 253 (M^+ +1), 236, 204, 159. (*Z*)-**6**: bp 130—135 °C/0.1 mmHg; $[\alpha]_D^{24}$ −390.8° (*c* 1.18, $CHCl_3$); IR (neat) 1720, 1660, 1600, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.36 (t, *J*=7 Hz, 3H), 2.03 (d, *J*=2 Hz, 3H), 2.40 (s, 3H), 4.33 (q, *J*=7 Hz, 2H), 6.50 (m, 1H), 7.28, 7.72 (ABq, *J*=8 Hz, 2×2H). Found: C, 61.8; H, 6.2%. Calcd for $C_{13}H_{16}O_3S$: C, 61.87; H, 6.40%; MS *m/z* 253 (M^+ +1), 236, 204, 159.

If the reaction conditions (−80 °C) are not maintained throughout, partial racemization occurs, resulting in low optically active (*E*)- and (*Z*)-**6**.

As indicated in the preliminary communication,[13] a Emmons-Horner condensation using NaH as a base gave the (*E*)- and (*Z*)-**6** in 23 and 10% yields, respectively. A variety of conditions were explored to optimize the yields. Finally, it was found that the reaction conducted by the use of *n*-BuLi as a base, at low temperature, gave slight satisfactory yields of (*Z*)-**6** (33%) and (*E*)-**6** (25%).

Diels-Alder Reaction of (*Z*)-6 and Cyclopentadiene. A mixture of freshly distilled cyclopentadiene (240 ml, 2.9 mol) and (*Z*)-**6** (22.13 g, 87.8 mmol, $[\alpha]_D^{26}$ −337° (*c* 1.0, $CHCl_3$)) was heated at 90 °C for 5 h in a pressure bottle tightly sealed with a stainless steel cap. Unreacted cyclopentadiene was removed under reduced pressure to give crude material, which was filtered by a silica-gel column (6×40 cm) in hexane. Elution with the solvent gave dicyclopentadiene. Elu-

tion was continued with ethyl acetate giving a mixture of **7**—**9** and recovered **6**. The HPLC analysis (hexane-ethyl acetate 1 : 1) of the crude product showed a mixture of 32 : 66 : 2 (**7** : **8** : **9**). Thus, the diastereomeric excesses of exo and endo sulfoxides were determined to be 100% and 94%, respectively. The crude mixture was chromatographed on silica gel (MPLC, 350 g) with hexane-ethyl acetate (1 : 3) to afford (*Z*)-**6** (1.084 g). Elution with ethyl acetate gave **7** (8.772 g, 31%), **8** (16.011 g, 57%), and **9** (0.848 g, 3%).

Ethyl (+)-(R)$_s$-(1*R*,4*S*)-*endo*-2-Methyl-*exo*-3-(*p*-tolylsulfinyl)bicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylate (7). mp 91 °C (hexane); $[\alpha]_D^{24}$ +60.2° (*c* 0.72, $CHCl_3$); IR (KBr) 1725, 1600, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.17 (s, 3H), 1.33 (t, *J*=7 Hz, 3H), 1.57 (br d, *J*=9 Hz, 1H), 2.23 (d, *J*=9 Hz, 1H), 2.25 (d, *J*=3 Hz, 1H), 2.45 (s, 3H), 3.1 (br s, 1H), 3.2 (br s, 1H), 4.24 (q, *J*=7 Hz, 2H), 6.12 (br s, 2H), 7.20, 7.47 (ABq, *J*=9 Hz, 2×2H). Found: C, 67.92; H, 6.94%. Calcd for $C_{18}H_{22}O_3S$: C, 67.88; H, 6.98%; MS *m*/*z* 319 (M^+ +1), 273, 179.

Ethyl (−)-(R)$_s$-(1*S*,4*S*)-*exo*-2-Methyl-*endo*-3-(*p*-tolylsulfinyl)bicyclo[2.2.1]hept-5-en-*endo*-2-carboxylate (8). mp 85—86 °C (hexane); $[\alpha]_D^{19}$ −4.82° (*c* 0.65, $CHCl_3$); IR (KBr) 1730, 1600, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.12 (*J*=8 Hz, 3H), 1.12 (s, 3H), 1.54 (s, 2H), 2.30 (s, 3H), 2.83 (s, 1H), 3.10 (d, *J*=4 Hz, 1H), 3.40 (s, 1H), 4.00 (m, 2H), 6.18 (dd, *J*=6, 3 Hz, 1H), 6.47 (dd, *J*=6, 3 Hz, 1H), 7.20, 7.70 (ABq, *J*=8 Hz, 2×2H). Found: C, 68.02; H, 6.98%. Calcd for $C_{18}H_{22}O_3S$: C, 67.88; H, 6.98%; MS *m*/*z* 319 (M^+ +1), 273, 179, 91.

Ethyl (+)-(R)$_s$-(1*R*,4*S*)-*exo*-2-Methyl-*endo*-3-(*p*-tolylsulfinyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylate (9). mp 89—90 °C (hexane); $[\alpha]_D^{27}$ +184.10° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 1730, 1590, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.34 (t, *J*=7 Hz, 3H), 1.42 (d, *J*=8 Hz, 1H), 1.62 (d, *J*=8 Hz, 1H), 1.70 (s, 3H), 2.24 (br s, 1H), 2.45 (s, 3H), 2.97 (br s, 1H), 3.06 (d, *J*=3 Hz, 1H), 4.26 (dq, *J*=7, 1 Hz, 2H), 6.18 (dd, *J*=6, 3 Hz, 1H), 6.32 (dd, *J*=6, 3 Hz, 1H), 7.38, 7.70 (ABq, *J*=8 Hz, 2×2H). Found: C, 67.63; H, 6.87%. Calcd for $C_{18}H_{22}O_3S$: C, 67.88; H, 6.98%; Exact mass Found: *m*/*z* 318.1311. Calcd for $C_{18}H_{22}O_3S$: M, 318.1288; MS *m*/*z* 319 (M^+ +1), 179, 151, 91.

Ethyl (−)-(1*R*,4*S*)-*exo*-2-Methyl-*endo*-3-(*p*-tolylthio)-bicyclo[2.2.1]heptane-*endo*-2-carboxylate (10). A mixture of **8** (3.59 g, 11.3 mmol) and 10% Pd on carbon (495 mg) in ethanol (45 ml) was evacuated, flushed with hydrogen and stirred vigorously under hydrogen atmosphere at room temperature for 7 h. The mixture was filtered through a short pad of Celite and the filter pad was washed with warm ethanol (4×25 ml). Solvent evaporation gave the dihydro sulfoxide (3.61 g, 100%). mp 67 °C (hexane); $[\alpha]_D^{26}$ −104.6° (*c* 1.01, $CHCl_3$); IR (melt) 1730, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.77 (s, 3H), 1.27 (t, *J*=7 Hz, 3H), 1.3—1.7 (m, 6H), 2.2 (br, 1H), 2.40 (s, 3H), 2.6 (m, 1H), 3.0 (br, 1H), 4.13 (q, *J*=7 Hz, 2H), 7.20, 7.67 (ABq, *J*=8 Hz, 2×2H). Found: C, 67.40; H, 7.53%. Calcd for $C_{18}H_{24}O_3S$: C, 67.47; H, 7.55%; MS *m*/*z* 321 (M^+ +1), 181, 153.

To a solution of the sufoxide obtained above (3.396 g, 10.6 mmol) in ethanol (30 ml) was added dropwise ca. 25% aq. $TiCl_3$ solution (8 ml, 13 mmol) at room temperature. The reaction mixture was stirred for 1 h and diluted with water (50 ml). Most of the ethanol was evaporated and the aqueous layer was extracted with ether (5×50 ml). Evaporation and purification by distillation afforded pure sulfide **10** (2.952 g, 92%). bp 110—113 °C/0.2 mmHg; $[\alpha]_D^{26}$ −7.32° (*c* 1.09, $CHCl_3$); IR (neat) 1725, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.2—1.8 (m, 6H), 1.30 (t, *J*=7 Hz, 3H), 1.38 (s, 3H), 2.2 (br s, 2H), 2.32 (s, 3H), 3.00 (dd, *J*=4, 2 Hz, 1H), 4.17 (q, *J*=7 Hz, 2H), 7.00, 7.27 (ABq, *J*=8 Hz, 2×2H). Exact mass Found: *m*/*z* 304.1462. Calcd for $C_{18}H_{24}O_2S$: M, 304.1497; MS *m*/*z* 304 (M^+), 236, 153, 91.

Ethyl (−)-(1*S*,4*R*)-*exo*-2-Methyl-3-oxobicyclo[2.2.1]-heptane-*endo*-2-carboxylate ((−)-11). A mixture of sulfide **10** (216 mg, 0.7 mmol) and NCS (513 mg, 3.8 mmol) in CCl_4 (6 ml) was refluxed for 30 min. The reaction mixture was filtered and the filtrate was concentrated to dryness. Without further purification the crude product was successively treated with $CuCl_2 \cdot 2H_2O$ (309 mg, 2 mmol), CuO (247 mg, 3.1 mmol), acetone (10 ml) and water (1 ml) to reflux for 20 min. The reaction mixture was then filtered through a short pad of Celite and the filtrate was concentrated. The residue was partitioned with ether (2×30 ml) and water (10 ml). The combined ether portions were washed with sat. brine, dried ($MgSO_4$) and concentrated. The crude product was purified by silica-gel chromatography(benzene and then ether) to give **11** (119 mg, 85%). A prolonged heating resulted in gradual decomposition of the product. **11**: bp 114—118 °C/7 mmHg; $[\alpha]_D^{26}$ −7.15° (*c* 1.55, $CHCl_3$); IR (neat) 1750, 1720 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.0—2.0 (m, 6H), 1.27 (t, *J*=8 Hz, 3H), 1.27 (s, 3H), 2.53 (br, 2H), 4.13 (q, *J*=8 Hz, 2H). Exact mass Found: *m*/*z* 196.110. Calcd for $C_{11}H_{16}O_3$: M, 196.110. In the NMR spectrum of (±)-**11**, the two enantiotopic tertiary methyl hydrogens resonate at 3.17 and 3.28 ppm due to (+)- and (−)-enantiomer, respectively, by adding a chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (Eu(hfc)$_3$). No such separation was observable under the same conditions (0.28 equiv used) in the spectrum of (−)-**11** derived from **10**.

Ethyl (−)-(1*R*,4*S*)-*exo*-2-Methyl-3-methylenebicyclo[2.2.1]-heptane-*endo*-2-carboxylate (13). A suspension of activated zinc dust (2.124 g, 32.5 mmol) and dibromomethane (1.2 ml, 17.1 mmol) in dry THF (10 ml) was treated with 1 M $TiCl_4$ solution in CH_2Cl_2 (3.8 ml, 3.8 mmol) at room temperature. Instantaneous reaction occurred under evolution of heat and the color changed to dark brown. After 20 min **11** (730 mg, 3.72 mmol) in dry THF (10 ml) was added by a syringe for 15 min. The suspension was stirred for 21 h at room temperature. The reaction mixture was diluted with ether (20 ml) and poured into 5% hydrochloric acid (15 ml). The aqueous layer was extracted with ether (5×20 ml). The extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification by chromatography on silica gel gave **13** (288 mg, 40%). bp 76—81 °C/13 mmHg; $[\alpha]_D^{29}$ −46.3° (*c* 0.75, $CHCl_3$); IR (neat) 1735, 1718, 1260, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.27 (t, *J*=7 Hz, 3H), 1.33 (s, 3H), 1.1—1.8 (m, 6H), 2.33 (br s, 1H), 2.73 (br s, 1H), 4.17 (q, *J*=7 Hz, 2H), 4.83 (s, 1H), 5.03 (s, 1H). Exact mass Found: *m*/*z* 194.1303. Calcd for $C_{12}H_{18}O_2$: M, 194.1306; MS *m*/*z* 194 (M^+), 149, 121, 93; R_f 0.44 (benzene).

(+)-(1*R*,4*S*)-*exo*-2-Methyl-3-methylenebicyclo[2.2.1]-heptane-*endo*-2-methanol (14). Diisobutylaluminium hydride (1 M in hexane, 3 ml, 3 mmol) was added slowly to a solution of **13** (288 mg, 1.48 mmol) in dry ether (5 ml) at −78 °C. The mixture was stirred for 1 h at that temperature and diluted with 5% hydrochloric acid (5 ml). The clear solution was extracted with ether (5×10 ml) and the extracts were washed with sat. brine and dried ($MgSO_4$). Evaporation gave **14** (226 mg, 100%) as an oil, which crystallized. bp 117—121 °C/63 mmHg; mp 74—79 °C (pentane); $[\alpha]_D^{24}$ +96.2° (*c* 0.85, $CHCl_3$); IR (neat) 3380, 1645 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ=1.12 (s, 3H), 1.0—2.0 (m, 6H), 2.13 (br s, 1H), 2.72 (br s, 1H), 3.50 (s, 2H), 4.47 (s, 1H), 4.80 (s, 1H). Found: C, 79.01; H, 10.41%. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59%; MS *m/z* 152 (M^+), 121, 79; R_f 0.1 (benzene).

(+)-(1*R*,4*S*)-*exo*-2-Methyl-3-methylenebicyclo[2.2.1]-heptane-*endo*-2-carbaldehyde (15). A mixture of PCC (1.084 g, 5.03 mmol), **14** (226 mg, 1.48 mmol) and Molecular Sieves 4A (822 mg) in dry CH_2Cl_2 (5 ml) was stirred vigorously for 30 min. The mixture was diluted with ether (15 ml) and the ether layer was filtered through a short pad of Florisil. This work-up was repeated three times and the filtrates were concentrated to give the aldehyde **15** (158 mg, 90%). bp 113—117 °C/80 mmHg; $[\alpha]_D^{28}$ +17.1° (*c* 1.46, $CHCl_3$) ; IR (neat) 1715, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.13 (s, 3H), 1.0—2.0 (m, 6H), 2.30 (br s, 1H), 2.83 (br s, 1H), 4.60 (s, 1H), 5.03 (s, 1H), 9.60 (s, 1H). Exact mass Found: *m/z* 150.1007. Calcd for $C_{16}H_{14}O$: M, 150.1043; MS *m/z* 150 (M^+), 149, 113, 57; R_f 0.52 (benzene).

(*E*)-Ethyl (−)-(1*R*,4*S*)-3-[*exo*-2-Methyl-3-methylenebicyclo[2.2.1]hept-*endo*-2-yl]-2-propenoate (16). To a solution of triethyl phosphonoacetate (0.6 ml, 3.02 mmol) in dry THF (3 ml) was added 1.62 M *n*-BuLi in hexane (1.8 ml, 2.92 mmol) at −78 °C. After 45 min the reaction mixture was added to a stirred solution of **15** (158 mg, 1.05 mmol) in dry THF (2 ml) by a cannula. The mixture was stirred at that temperature for 30 min. Diluted hydrochloric acid was poured into the mixture and the aqueous layer was extracted with ether (5×10 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude oil was purified by chromatography (ether/pentane 1 : 4) to give **16** (223 mg, 96%). bp 116—121 °C/15 mmHg; $[\alpha]_D^{28}$ −132.5° (*c* 1.12, $CHCl_3$); IR (neat) 1719, 1642, 1280, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.17 (s, 3H), 1.30 (t, *J*=7 Hz, 2H), 1.0—2.0 (m, 6H), 2.10 (br s, 1H), 2.77 (br s, 1H), 4.18 (q, *J*=7 Hz, 2H), 4.52 (s, 1H), 4.97 (s, 1H), 5.92 (d, *J*=16 Hz, 1H), 6.93 (d, *J*=16 Hz, 1H). Exact mass Found: *m/z* 220.1487. Calcd for $C_{14}H_{20}O_2$: M, 220.1462; MS *m/z* 220 (M^+), 191, 147, 91; R_f 0.50 (benzene).

Ethyl (+)-(1*R*,4*S*)-3-[*exo*-2-Methyl-3-methylenebicyclo-[2.2.1]hept-*endo*-2-yl]propanoate (17). A mixture of **16** (281 mg, 1.28 mmol), triethylsilane (0.3 ml, 1.9 mmol) and a catalytic amounts of tris (triphenylphosphine) chlororhodium was heated at 90 °C for 20 min. After cooling, ethanol (0.5 ml) was added to the mixture. The mixture was concentrated and the crude oil was chromatographed (ether-pentane 1 : 5) to give **17** (283 mg, 100%). bp 140—144 °C/15 mmHg; $[\alpha]_D^{26}$ +25.8° (*c* 2.45, $CHCl_3$); IR (neat) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00 (s, 3H), 1.27 (t, *J*=7 Hz, 3H), 1.0—2.6 (m, 11H), 2.70 (br s, 1H), 4.16 (q, *J*=7 Hz, 2H), 4.53 (s, 1H), 4.78 (s, 1H). Exact mass Found: *m/z* 222.1588. Calcd for $C_{14}H_{22}O_2$: M, 222.1619; MS *m/z* 223, 222 (M^+), 93, 91; R_f 0.52 (benzene).

(+)-(1*R*,4*S*)-*exo*-2-Methyl-3-methylenebicyclo[2.2.1]-hept-2-ene-*endo*-3-propanol (18). To a solution of **17** (397 mg, 1.79 mmol) in dry ether (7 ml) was added 1 M DIBAL in hexane (5.4 ml, 5.4 mmol) at −78 °C and the mixture was stirred for 2.5 h. Diluted hydrochloric acid was added to the mixture and the aqueous layer was extracted with ether (5×10 ml). The combined extracts were dried ($MgSO_4$) and concentrated. The crude oil was purified by chromatography (ether/pentane 1 : 1) to give **18** (298 mg, 93%). bp 126—139 °C/11 mmHg; $[\alpha]_D^{25}$ +48.3° (*c* 1.13, $CHCl_3$); IR (neat) 3325, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.01 (s, 3H), 1.1—1.6 (m, 10H), 2.00 (br s, 1H), 2.69 (br s, 1H), 3.64 (m, 2H), 4.48 (s, 1H), 4.72 (s, 1H). Exact mass Found: *m/z* 180.1513. Calcd for $C_{14}H_{20}O_2$: M, 180.1513; MS *m/z* 180 (M^+), 136; R_f 0.10 (benzene).

(+)-(1*R*,4*S*)-*exo*-2-Methyl-3-methylenebicyclo[2.2.1]-hept-2-ene-*endo*-3-propanal (19). A mixture of PCC (981 mg, 4.55 mmol), **18** (298 mg, 1.66 mmol) and Molecular Sieves 4A (1 g) in dry CH_2Cl_2 (15 ml) was stirred vigorously for 1 h. The mixture was diluted with ether (45 ml) and the ether layer was filterd through a short pad of Florisil (ca. 10 g). The black residue was washed with ether (3×10 ml) and the combined filtrates were concentrated to give **19** (284 mg, 96%). bp 98—101 °C/15 mmHg; $[\alpha]_D^{25}$ +30.83° (*c* 1.10, $CHCl_3$); IR (neat) 1725, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00 (s, 3H), 1.00—1.87 (m, 8H), 1.97 (br s, 1H), 2.27—2.70 (m, 2H), 2.70 (br s, 1H), 4.52 (s, 1H), 4.77 (s, 1H), 9.80 (t, *J*=1.5 Hz, 1H). Exact mass Found: *m/z* 178.1356. Calcd for $C_{14}H_{18}O_2$: M, 178.1356; MS *m/z* 178 (M^+), 163, 94, 93, 91; R_f 0.52 (benzene).

(+)-*epi*-β-Santalene (4). To a suspension of isopropyltriphenylphophonium bromide (358 mg, 0.93 mmol) in dry THF (7 ml) was added dropwise 1.62 M *n*-BuLi in hexane (1.7 ml, 2.75 mmol) at 0 °C. After an additional 10 min **19** (102 mg, 0.57 mmol) in dry THF (3 ml) was added to the red suspension. The mixture was stirred for 18 h at room temperature and poured into water (10 ml). The aqueous layer was extracted with petroleum ether (5×10 ml). The combined extracts were washed with water (10 ml), sat. brine and dried ($MgSO_4$). The solvent was evaporated and the crude oil was purified by chromatography (petroleum ether) to give (+)-*epi*-β-santalene (**4**)(67 mg, 57%). bp 94—115 °C/2—5 mmHg; $[\alpha]_D^{27}$ +26.35° (*c* 0.39, $CHCl_3$) (lit,[4] $[\alpha]_D^{22}$ +23.3° (*c* 4.12, $CHCl_3$), $[\alpha]_D^{27}$ +26.9° (*c* 2.6, $CHCl_3$)); IR (neat) 1655, 1445, 1375, 1103, 879 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.02 (s, 3H), 1.00—2.08 (m, 11H), 1.62 (s, 3H), 1.68 (s, 3H), 2.67 (br s, 1H), 4.46 (s, 1H), 4.70 (s, 1H), 5.12 (br t, *J*=7 Hz, 1H). Exact mass Found: *m/z* 204.1901. Calcd for $C_{15}H_{25}$: M, 204.1878; MS *m/z* 204 (M^+), 161, 105, 91; R_f 0.73 (petroleum ether).

Ethyl (+)-(1*S*,4*R*)-*endo*-2-Methyl-3-(*p*-tolylthio)bicyclo[2.2.1]heptane-*exo*-2-carboxylate (20). As described above for **8**→**10**, the cycloadduct **7** (415 mg, 1.31 mmol) in ethanol (12 ml) was hydrogenated to give the dihydro sulfoxide (420 mg, 100%). mp 95—96 °C (diisopropyl ether); $[\alpha]_D^{25}$ +28.14° (*c* 1.19, $CHCl_3$); IR (KBr) 1725, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.3—1.8 (m, 6H), 1.13 (s, 3H), 1.30 (t, *J*=7 Hz, 3H), 2.40 (s, 3H), 2.8 (br s, 1H), 2.0—3.0 (m, 2H), 4.17 (q, *J*=7 Hz, 2H), 7.27, 7.60 (ABq, *J*=8 Hz, 2×2H). Found: C, 67.26; H, 7.54%. Calcd for $C_{18}H_{24}O_3S$: C, 67.47; H, 7.55%; MS *m/z* 321 (M^+ +1), 304, 153.

The sulfoxide (439 mg, 1.37 mmol) was treated as decribed for **10**, giving the sulfide **20** (384 mg, 92%). mp 39—41.5 °C (sublimed); bp 123—125 °C/0.1 mmHg; $[\alpha]_D^{24}$ −14.87° (*c* 1.30, $CHCl_3$); IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.0—1.7 (m, 5H), 1.23 (t, *J*=7 Hz, 3H), 1.37 (s, 3H), 2.30 (s, 3H), 2.0—2.6 (m, 3H), 2.70 (d, *J*=2 Hz, 1H), 4.10 (q, *J*=7 Hz, 2H), 7.03, 7.27 (ABq, *J*=8 Hz, 2×2H). Found: C, 71.30; H, 7.87%. Calcd for $C_{18}H_{24}O_2S$: C, 71.07; H, 7.95%; MS *m/z* 304 (M^+), 143.

Ethyl (−)-(1*S*,4*R*)-*endo*-3-Oxobicyclo[2.2.1]heptane-*exo*-2-carboxylate (21). A mixture of sulfide **20** (398 mg, 1.29 mmol), NCS (886 mg, 6.64 mmol), and CCl_4 (25 ml) was heated to reflux for 2 h. After cooling, the reaction mixture was filtered and the filtrate was concentrated to dryness.

Without further purification, the crude product was successively treated with $CuCl_2 \cdot 2H_2O$ (941 mg, 6.17 mmol), CuO (935 mg, 11.8 mmol), acetone (17 ml) and water (1.7 ml) to reflux for 4 h. The mixture was filtered through a short pad of Celite and the filtrate was concentrated. The residue was partitioned with Et_2O and H_2O. The Et_2O layer was washed with satd brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica (PhH and then Et_2O) and distilled to give **21** (183 mg, 72%). bp 150—157 °C/5 mmHg; $[\alpha]_D^{25}$ −93.7° (*c* 0.87, $CHCl_3$); IR (neat) 2990, 1760, 1725, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.25 (s, 3H), 1.28 (t, *J*=7 Hz, 3H), 1.4—2.3 (m, 6H), 2.58 (br, 1H), 2.77 (br, 1H), 4.13 (q, *J*=7 Hz, 2H). Found: C, 66.86; H, 8.28%. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%. Exact mass Found: *m/z* 196.1109. Calcd for $C_{11}H_{16}O_3$: M, 196.1099; MS *m/z* 196 (M^+), 168, 139, 95, 67.

(−)-(1*S*,4*R*)-*endo*-2-Hydroxy-*exo*-3-methylbicyclo[2.2.1]heptane-*endo*-2-methanol (22). A solution of keto ester **21** (2.328 g, 12 mmol) in dry Et_2O (10 ml) was added to a suspension of $LiAlH_4$ (1.163 g) in dry Et_2O (30 ml) at 0 °C. The mixture was stirred for 3 h at room temperature. The excess of reagent was destroyed by addition of a minimal amount of H_2O. The mixture was filtered and the filtrate was concentrated under vacuum. Purification by crystallization from *i*-Pr_2O afforded diol **22** (1.282 g, 69%). mp 108—110 °C; $[\alpha]_D^{25}$ −8.55° (*c* 0.52, $CHCl_3$); IR (KBr) 3320, 2975, 1470, 1355 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.92 (s, 3H), 1.0—2.0 (m, 7H), 2.32 (br, 1H), 2.55 (br, 2H, OH), 3.35 (s, 2H), 3.75 (d, *J*=4 Hz, 1H). Found: C, 69.43; H, 10.23%. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32%; MS *m/z* 138 (M^+ −18), 123, 107, 95, 69, 67.

(−)-(1*S*,4*R*)-*endo*-2-Methyl-3-oxobicyclo[2.2.1]heptane-*exo*-2-carbaldehyde (23). To a solution of CH_2Cl_2 (25 ml) and oxalyl dichloride (0.07 ml, 0.8 mmol) was added dropwise DMSO (0.12 ml, 1.7 mmol) in CH_2Cl_2 (0.5 ml) at −50—60 °C. The mixture was stirred for 3 min and the diol **22** (107 mg, 0.69 mmol) in CH_2Cl_2 (1 ml) was added dropwise over a period of 5 min. The reaction mixture was stirred for an additional 20 min. Triethylamine (4.5 ml, 32 mmol) was added and the mixture was stirred for 20 min. After diluting with H_2O (10 ml) the aqueous layer was extracted with CH_2Cl_2 (3×15 ml). The combined extracts were washed with dil HCl, sat. brine, dried ($MgSO_4$) and concentrated. Purification of the oily product by distillation gave keto aldehyde **23** (100 mg, 96%). bp 65—75 °C/6 mmHg; $[\alpha]_D^{24}$ −329.1° (*c* 0.43, $CHCl_3$); IR (neat) 2720, 1750, 1710 cm^{-1}; ^1H NMR (CCl_4) δ=1.20 (s, 3H), 1.3—2.1 (m, 6H), 2.57 (br, 1H), 2.83 (br, 1H), 9.36 (s, 1H). Found: C, 68.77; H, 8.03%. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95%. Exact mass Found: *m/z* 152.0841. Calcd for $C_9H_{12}O_2$: M, 152.0837; MS *m/z* 152 (M^+), 124, 109, 95, 67.

(−)-(1*S*,4*R*)-*endo*-2-Methyl-3-oxobicyclo[2.2.1]heptane-*exo*-2-carbaldehyde Dimethyl Acetal (24). Keto aldehyde **23** was dissolved in a 0.2 M methanolic solution of $CeCl_3 \cdot 7H_2O$ (1.5 ml, 0.3 mmol) and trimethyl orthoformate (0.166 ml, 1.5 mmol) was added to the solution. The reaction mixture was allowed to stand for 3 days at room temperature. After addition of sat. $NaHCO_3$ (3 ml), the mixture was extracted with Et_2O (3×15 ml) and the extracts were concentrated. Purification by distillation afforded acetal **24** (43 mg, 72%, purity >86% from vpc). An analytical sample was obtained by redistillation. bp 65—75 °C/3 mmHg; $[\alpha]_D^{24}$ −62.6° (*c* 0.71, $CHCl_3$); IR (neat) 1740, 1445, 1110, 1065 cm^{-1}; ^1H NMR (CCl_4) δ=0.95 (s, 3H), 1.12—1.87 (m, 6H), 2.37 (br, 1H), 2.62 (br, 1H), 3.32 (s, 3H), 3.38 (s, 3H), 4.12 (s, 3H). Found: C, 66.49; H, 9.24%. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%; MS *m/z* 198 (M^+), 167, 139, 107, 75, 67.

In the ^1H NMR, racemic **24** (prepared from (±)-**21**) was resolved to a pair of singlets due to the tertiary methyl at 2.97 and 3.10 ppm using a chiral shift reagent Eu(hfc)$_3$ (1.67 equiv used). The acetal (−)-**24** showed the tertiary methyl signal at 2.97 ppm. The peak of the corresponding enantiomer was hardly observed within the limit of detection.

(−)-(1*S*,4*R*)-*endo*-2-Methyl-3-methylenebicyclo[2.2.1]heptane-*exo*-2-carbaldehyde Dimethyl Acetal (25). A suspension of activated Zn (129 mg, 2 mg atom) and CH_2Br_2 (0.04 ml, 0.57 mmol) in dry THF (0.5 ml) was treated with 1 M $TiCl_4$ in CH_2Cl_2 (0.4 ml, 0.4 mmol) at room temperature. During the reaction the color changed to dark brown. After 15 min, keto acetal **24** (72 mg, 0.36 mmol) in dry THF (0.5 ml) was added dropwise over a period of 15 min via a syringe. The mixture was stirred for 21 h at ambient temperature. The reaction mixture was partitioned with CH_2Cl_2 (5 ml) and sat. $NaHCO_3$ (5 ml). The aqueous layer was extracted with CH_2Cl_2 (3×10 ml). The combined extracts were concentrated to dryness. Purification by chromatography (pentane) afforded acetal **25** (43 mg, 60%, 51% purity from vpc). An analytical sample was obtained by a Kugelrohr distillation. bp 120—125 °C/42 mmHg; $[\alpha]_D^{24}$ −119.3° (*c* 0.91, $CHCl_3$); IR (neat) 1655, 1450, 1190, 1110, 1070, 985, 890 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.08 (s, 3H), 1.0—1.9 (m, 6H), 2.32 (br, 1H), 2.69 (br, 1H), 3.49 (s, 3H), 3.48 (s, 3H), 4.01 (s, 1H), 4.73 (s, 1H), 4.84 (s,1H). Found: C, 70.40; H, 10.00%. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27%; MS *m/z* 167 (M^+ −29), 149, 93, 75.

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