The Total Synthesis of (±)-Pentalenolactone E Methyl Ester Using a Stepwise [3+2] Process

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Neste trabalho apresentamos os resultados detalhados de nossa síntese total do éster metílico da pentalactona E. A síntese constitui aplicação de uma rota geral para ciclopentenos, utilizando um processo [3+2]. Essa estratégia para a construção de anéis de cinco membros fundamenta-se na geração *in situ* do enolato de um γ -oxo-éster a partir de um éster β -(sililoxi)ciclopropânico. O sistema 1,3-bifuncional (enolato do γ -oxo-éster), ao reagir com um aceptor de Michael de 2 carbonos, tal como o sal de [α -(feniltio)vinil]-fosfônio, leva a um ciclopenteno, o qual é facilmente transformado na ciclopentanona correspondente. Utilizando essa metodologia na etapa-chave, a síntese do éster metílico da pentalenolactona E foi efetuada em 13 etapas, com rendimento total de 5%.

In this work we give a full account of our total synthesis of pentalenolactone E methyl ester. The synthesis is made through an application of an efficient and general route to annulated cyclopentenones, utilizing a stepwise [3+2] process. This strategy for the construction of five-membered rings relies on the *in situ* generation of a γ -oxo ester enolate from β -(silyloxy)cyclopropyl ester. The 1,3-bifunctional system (γ -oxo ester enolate), when combined with a two carbon acceptor such as [α -(phenylthio)vinyl]-phosphonium salt, leads to a cyclopentene which is readily transformed into its cyclopentanone analog. By using this methodology in a key step the total synthesis of pentalenolactone E methyl ester was achieved in 13 steps, with a 5% overall yield.

Keywords: pentalenolactone E methyl ester, pentanellation

Introduction

About 20 years ago Shibata¹ and coworkers isolated the first natural product containing a triquinane structure, which was named retigeranic acid (1).

Since then a number of triquinanic compounds have been isolated from natural sources and identified². Among the well known triquinanes are the isomeric triquinanes A (tricyclo[6.3.0.0]^{2,6}undecane) and B (tricyclo[6.3.0.0]^{4,8}undecane), which represent the basic framework of important biologically active sesquiterpenoids found in the hirsutene (linear) and pentalenene (angular) families (Fig. 1). These compounds have attracted the attention of several research groups as models for synthetic³ and biosynthetic⁴ studies. These efforts are justified in view of the biological activity exhibited by some of these substances⁵. The linearly fused tricyclopentanoids (Type A, Fig. 1), those of the

Figure 1. Naturally occurring triquinanes.

hirsutene family in particular, have received more attention due to the promising antitumoral activity of the corioline⁶. Less attention has been given to the triquinanes with three angularly fused rings (Type B, Fig. 1). Although the important antibiotic agent pentalenolactone (5) has been classified in terms of a bicyclic[3.3.0]octane structure rather than as a tricyclic[6.3.0.0]^{4,8} framework with an expanded δ-lactone ring, biosynthetic studies demonstrated that pentalenolactone (5)⁷ and its co-metabolites (pentalenic acid (10)⁸ and pentalenolactones E (2)⁹, G (3)¹⁰ and H (4)⁸) can present pentalenene (9) as a key intermediate^{4c,11,12}.

The isolation of pentalenolactone was first reported in 1957 by Celmer^{7a} from a culture of *Streptomyces*. The substance named PA-138 was reported to exhibit antibiotic activity against pathogenic and saprophytic fungus and gram-positive and gram-negative bacteria. In 1969, Takeuchi reported the isolation of PA-132 from *Streptomyces* sp n^o 8403-MC^{7b}, which was shown to inhibit the

synthesis of nucleic acids in bacteria cells. This substance, obtained as a white hygroscopic powder, was named pentalenolactone. Preliminary chemical and spectroscopic studies led to the assignment of Structure **6** to this substance.

Later, a group from the UpJohn Company^{7c,d} reported the isolation of pentalenolactone from fermentation cultures of *Streptomyces* UC 5319. The assignment of the structure was then revised. Crystallographic analysis^{7d} showed the correct structure to be **5**.

More recently a number of analogs of pentalenolactone have been isolated from natural sources⁸⁻¹⁰ (Fig. 2).

Figure 2. Pentalenolactones.

The biosynthetic pathway leading to pentalenolactone was studied by Cane and coworkers^{4c}. In 1983 the preparation of an extract from *Streptomyces* was reported, free of cells, which catalyses the cyclization of *trans,trans*-farnesyl pyrophosphate (**8**) to pentalene (**9**), the hydrocarbon precursor of the pentalenolactone antibiotics^{4c} (Scheme 1).

Pentalenolactone (**5**) is probably formed from the pentalenic acid (**10**) through an oxidative cleavage of the C₁₁-C₁₂ bond of ring C, and a Wagner-Meerwein rearrangement of a methyl group from carbon 2 to carbon 1 of ring A¹² (Scheme 2).

As previously mentioned, the natural products with fused five membered rings attracted the attention of organic chemists for synthetic studies³. Among the sesquiterpenes pentalenolactone (**5**), pentalenolactone E (**2**), G (**3**) and H (**4**), compound **2** is the one that can be considered representative, and thus was chosen as a target in our attempt to establish a general synthetic route to the pentalenolactone series. While several syntheses for pentalenolactone E (**2**) have been reported¹³, the route described here features an

efficient one-pot cyclopentanellation process, ester differentiation leading to the γ -lactone, and a new sequence to the α,β -unsaturated methyl ester from the cyclopentanone¹⁴.

Synthetic background

In recent years a great number of general methods giving access to cyclopentanoid structures have been reported in the literature³. Some time ago, one of us devised a method for constructing functionalized cyclopentene rings via a [3+2] cyclopentanellation, employing the treatment of a highly functionalized cyclopropane **11** with a vinyl(thiophenyl)triphenylphosphonium salt **13** (Scheme 3)¹⁵.

The enolate **12**, produced by the fluoride ion attack at the silyl ether **11**, undergoes a Michael-type addition to the vinylphosphonium salt **13**, giving the phosphorane **14**. This reacts intramolecularly via a Wittig reaction, leading to the cyclic vinyl sulfide **15**. A mixture of isomeric products at the α position of the carboethoxy group was formed, indi-

Scheme 1.

Scheme 2.

Scheme 3.

cating the isomerization of the carbanion during the reaction. The *syn:anti* ratio reflects the relative stability of the isomers.

Retrosynthetic analysis

With these facts in mind we proposed the retrosynthetic analysis outlined in Scheme 4 for pentalenolactone E methyl ester (16).

The penultimate step of our synthesis was planned to be the introduction of the unsaturated methyl ester function, through the α -functionalization of the keto group of 17, followed by ketone function reduction and H_2O elimination. The failure of this sequence led us to develop a new strategy to obtain the α,β -unsaturated ester, which is described later. Construction of the δ -lactone ring was based on the different reactivity of the ester groups of intermediate 18; selective reduction of the ethyl ester to an alcohol

followed by lactonization should give 17. The lactonization agent (trifluoroacetic acid) should transform the vinylsulphide group of 18 into the keto group of 17. The intermediate 18 should originate from the highly functionalized cyclopropane 19 by means of the pentanellation sequence described in Scheme 3. Compound 20 should be prepared from 21¹⁶ using known methods¹⁵.

Experimental

General

All reactions were carried out under a nitrogen atmosphere. Solvents were purified according to the literature³¹. Yields were calculated for material judged homogeneous by TLC and NMR. TLC was performed on 250 μ m plates of Analtech silica, visualizing with a 254 nm UV lamp and with I_2 vapor or an acidic solution of vanillin. Column chromatography was performed with 40 μ m Baker silica

Scheme 4.

gel slurry packed in glass columns. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^1H -NMR) were recorded on a Bruker AC-80 (80 MHz), AM-300 (300 MHz) or WM 360 (360 MHz) instrument. The chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Carbon nuclear magnetic resonance spectra (^{13}C -NMR) were obtained at 75.4 MHz on a Bruker AM-300 or at 90.4 MHz on a Bruker WM-360 instrument, and are reported (ppm) relative to the center line of a triplet at 77.0 ppm for CDCl_3 . Infrared (IR) spectra were measured with a Nicolet 5-DX or a Perkin-Elmer 1750 infrared spectrometer. Low-resolution mass spectra were determined on a Finnigan 4021 GCMS/DS spectrometer. High-resolution mass spectra were determined on a V6 70-250-spectrometer. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Arbor, Michigan.

2,2-Dimethyl-4-Pental (31)¹⁶

Allyl alcohol (87 g; 1.5 mol), isobutyraldehyde (162 g; 2.25 mol) and *p*-toluenesulphonic acid (0.5 g) in *p*-cymene (300 mL) were heated under reflux for 48 h in a Dean-Stark apparatus. After the formation of 27 mL of water the Dean-Stark apparatus was replaced by a distillation head equipped with an efficient vigreux column, and the mixture was carefully distilled to give 2,2-dimethyl-4-pental (31). Yield: 150 g (90%); b.p.: 124-126 °C / 760 mmHg.

2,2-Dimethyl-4-keto-pentanal (32)¹⁶

A mixture of cuprous chloride (9.9 g; 100 mmol) and palladium chloride (0.354 g; 2 mmol) was stirred at room temperature in DMF (250 mL) and water (100 mL), while oxygen was bubbled through the suspension for 2 h. To this suspension was added 2,2-dimethyl-4-pental (31) (50 g; 0.5 mol). The mixture was stirred for 36 h at room temperature while oxygen was bubbled through. Then the mixture was diluted with water (500 mL) and the aqueous phase was extracted with diethyl ether (5 x 100 mL). The aqueous phase was acidified with 6 N HCl and extracted with ether. The combined ether extracts were washed with brine (3x100 mL), dried with MgSO_4 and filtered, and the solvent was removed in a rotatory evaporator. The residue was distilled under reduced pressure. Yield: 42.3 g (66%); b.p.: 84-86 °C / 20 mmHg.

4,4-Dimethylcyclopent-2-en-1-one (21)¹⁶

2,2-dimethyl-4-keto-pentanal (32) (30.4 g; 238 mmol) was added to a mixture of 5% aqueous KOH (100 mL), THF (100 mL) and diethyl ether (200 mL) purged with nitrogen for 1 h at 0 °C. The mixture was heated under reflux for 48 h, cooled, and then the phases were separated. The aqueous phase was saturated with NaCl. The mixture was extracted with diethyl ether (2 x 100 mL), the com-

bined ether extracts were washed with a saturated solution of NaCl (2 x 50 mL), dried with MgSO_4 , and filtered, and the solvent was evaporated in a rotatory evaporator. The residue was distilled under reduced pressure. Yield: 21.4 g (82%); b.p.: 60-62 °C / 20 mmHg.

4,4-Dimethyl-1-triethylsilyloxycyclopentene (22)¹⁷

Tris(triphenylphosphine)rhodium chloride (60 mg) was added to a solution of 4,4-dimethylcyclopent-2-en-1-one (21) (5.5 g; 50 mmol) and triethylsilane (6.97 g; 60 mmol; 1.2 equivalents) in dry benzene (50 mL) previously purged with dry argon for 1 h at 0 °C, and the mixture was magnetically stirred under nitrogen for 3-4 h at 70 °C (bath temperature). Then the solvent was removed, and the residue was dissolved in petroleum ether (50 mL) and filtered through a column containing Florisil. Evaporation of the solvent gave a yellow oil, which was purified on a silica gel column [hexane : ethyl acetate (15/1)], or by distillation at reduced pressure, to give a colorless oil. Yield: 9.0 g (80%); b.p.: 69-70 °C / 0.5 mmHg; IR (cm^{-1}): 2955, 2878, 1646, 1461, 1227, 922, 788; ^1H -NMR, 80 MHz (CDCl_3) δ : 0.55-1.10(m, 15H), 1.08(s, 6H), 2.05(s, 4H), 4.5(s, 1H).

(1 α ,3 α)-2 α (β)-Carbo-*tert*-butoxy-5,5-dimethyl-1 β -*t*-riethylsilyloxy-bicyclo [3.1.0]hexane (23)¹⁵

A solution of *t*-butyldiazoacetate (35.5 g; 250 mmol; 2.5 equivalents) in dry benzene (100 mL) was added dropwise over a period of 10 h to a stirred suspension of the enol ether 22 (23.7 g; 105 mmol) and CuSO_4 (400 mg) at 90 °C under nitrogen. After the completion of the addition the stirring continued at 70 °C for 10 h. The solvent was removed in a rotatory evaporator and the residue purified by a silica gel column to give 23 as a colorless oil.

Compound 23 was obtained as a mixture of diastereomers in a 1 : 1 syn/anti ratio determined by the relative integral of the α -carbo-*tert*butoxy signal in the ^1H -NMR spectrum of the mixture, and was used as such for further transformations. Analytically pure samples of the two diastereomers were obtained by silica gel column chromatography, and used for a detailed ^1H - and ^{13}C -NMR analysis. Yield: 33.16 g (93%, mixture of 23a and 23b); IR (cm^{-1}): 2953, 2937, 2877, 1720, 1242, 1133; mass spectrum (EI) m/z (rel intensity) 340(0.59), 325(0.81), 284(4.7), 269(48.38), 239(31.60), 137(66.78), 115(26.07), 87(75.12), 59(100); ^1H -NMR, 300 MHz (CDCl_3) δ : 23a 0.64(q, 6H, J = 8 Hz), 0.96(s, 3H), 0.97(t, 9H, J = 8 Hz), 1.10(s, 3H), 1.45(s, 1H), 1.60(d, 1H, J = 4.1 Hz), 1.38(dd, 1H, J = 13.5, 0.8 Hz), 1.97(dd, 1H, J = 13.5, 4.0 Hz), 2.0(s, broad, 2H), 2.13(1H, J = 4.2, 0.8 Hz); 23b 0.62(q, 6H, J = 7.9 Hz), 0.95(t, 9H, J = 7.9 Hz), 0.99(s, 3H), 1.16(s, 3H), 1.46(s, 9H), 1.5-1.7(m, 2H), 1.8(d, 1H, J = 13.4 Hz), 1.92-2.0(m, 2H), 2.23(d, 1H, J = 13.5 Hz); ^{13}C -NMR, 75.4MHz (CDCl_3) δ : 23a 5.5, 6.8, 28.3, 31.1, 33.3, 34.1,

36.7, 38.6, 43.2, 51.7, 72.9, 79.7, 168.7; **23b** 5.2, 6.6, 26.4, 28.4, 31.2, 34.2, 36.9, 37.7, 46.5, 47.0, 73.5, 79.8, 169.8; Elemental analysis: calculated for $C_{19}H_{36}SiO_3$ C = 67.00%, H = 10.65%; found C = 67.19%, H = 10.72%.

2-Carbo-tert-butoxy-methyl-4,4-dimethyl-cyclopentanone (20)³⁰

The $Et_3N \cdot HF$ adduct (2.67 g; 24 mmol; 1.6 equivalents) was added to a solution of **23** (5.10 g; 15 mmol) in dry THF (30 mL) at 0 °C under nitrogen. The mixture was stirred at room temperature for 4 h and the reaction was monitored by TLC. A saturated aqueous solution of $NaHCO_3$ (30 mL) was added to the reaction mixture, the phases were separated, and the aqueous phase was extracted with diethyl ether (3x20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After filtration the solvent was evaporated and the residue was purified by column chromatography on silica gel [hexane : ethyl acetate (9 : 1)]. The ketoester **20** was obtained as a colorless oil at room temperature, which crystallizes when maintained in a freezer. Yield: 2.97 g (87%); IR (cm^{-1}): 2955, 2933, 1742, 1729, 1367, 1158, 1129, 850; mass spectrum (EI) m/z (rel intensity) 226(0.01), 170(8.66), 153(17.04), 137(3.33), 111(4.98), 83(17.64), 57(100); ^1H -NMR, 300 MHz ($CDCl_3$) δ : 1.08(s, 3H), 1.19(s, 3H), 1.44(s, 9H), 1.55(dd, 1H, $J = 12.5$ Hz), 2.03(ddd, 1H, $J = 12.2, 8.2, 1.8$ Hz), 2.14(AB quartet, 2H, $J_{AB} = 19.0$ Hz), 2.35(dd, 1H, $J = 16.0, 7.7$ Hz), 2.6-2.75(m, 2H); ^{13}C -NMR, 75.4 MHz ($CDCl_3$) δ : 27.93, 28.09, 29.77, 34.01, 35.84, 43.32, 44.75, 52.66, 80.71, 171.19, 219.03; Elemental analysis: calculated for $C_{13}H_{22}O_3$ C = 68.99%, H = 9.79%; found C = 68.78%, H = 9.84%.

2-Carbo-tert-butoxy-methyl-4,4-dimethyl-1-trimethylsilyloxy-cyclopentene (24)¹⁹

The ketoester **20** (1.84 g; 8 mmol) was added to a solution of trimethylsilylchloride (1.73 g; 13.6 mmol; 1.7 equivalents) and Et_3N (2.23 mL; 16 mmol; 2 equivalents) in dry DMF (16 mL). The mixture was refluxed under magnetic stirring for 4 h (the bath temperature must be kept below 135 °C) and then cooled to room temperature. Ice cooled aqueous saturated $NaHCO_3$ was added to the mixture (50 mL) which was extracted with hexane (3 x 30 mL). The organic phase was dried with $MgSO_4$ and filtered, and the solvent was removed in a rotatory evaporator under vacuum. The residue was purified by flash chromatography in a silica gel column [hexane - ethyl acetate (9 : 1)], leading to a colorless oil. The product is unstable and decomposes even under refrigeration. Yield: 1.77 g (75%); IR (cm^{-1}): 3005, 2977, 2955, 2840, 1733, 1688, 1366, 1253, 1168, 1151, 881; mass spectrum (EI) m/z (rel intensity) 298(4.3), 242(16.13), 227(4.46), 197(48.72), 183(3.71), 151(23.67),

73(100); ^1H -NMR, 300 MHz ($CDCl_3$) δ : 0.20(s, 9H), 1.10(s, 6H), 1.45(s, 9H), 2.10(s, broad, 2H), 2.14(s, broad, 2H), 2.93(s, 2H); ^{13}C -NMR, 75.4 MHz ($CDCl_3$) δ : 0.5, 28.2, 30.3, 34.0, 34.8, 46.6, 48.9, 80.0, 109.4, 147.0, 170.9; Elemental analysis: calculated for $C_{16}H_{30}SiO_3$ C = 64.38%, H = 10.12%; found C = 64.42%, H = 10.20%.

2- α -(β)-Carboethoxy-3 β -carbo-tert-butoxy-methyl-5,5-dimethyl-1b-trimethylsilyloxy-bicyclo-[3.1.0]-hexane (19)¹⁵

A solution of ethyldiazoacetate (2.28 g; 20.0 mmol, 4 equivalents) in dry benzene (10 mL) was added dropwise over a 6 h period to a stirred suspension of the silylenol ether **24** (1.59 g; 5.3 mmol) and $CuSO_4$ (15 mg) at 95 °C under nitrogen. After the completion of the addition, stirring was maintained for 10 h at 70 °C. The solvent was removed in a rotatory evaporator and the residue purified by column chromatography [hexane/ethyl acetate (15 : 1)] giving a colorless oil. The cyclopropane was obtained as a 2 : 1 mixture of diastereomers (*syn* : *anti*), which was used for further transformations. Analytically pure samples were obtained by column chromatography separation. Yield: 1.67 g (82%); IR (cm^{-1}): 2978, 2973, 2957, 1732, 1368, 1251, 1173, 1149, 843; mass spectrum (EI) m/z (rel intensity) 328(1.28), 311(5.85), 255(41.40), 149(16.89), 73(79.43), 57(100); ^1H -NMR, 300 MHz ($CDCl_3$) δ : **19a** 0.11(s, 9H), 0.98(s, 3H), 1.08(s, 3H), 1.25(t, 3H, $J = 7.2$ Hz), 1.41(s, 9H), 1.77(s, 1H), 1.71 and 1.77(AB quartet, 2H, $J_{AB} = 13.3$ Hz), 2.43 and 3.30(AB quartet, 2H, $J_{AB} = 17.1$ Hz), 4.06(q, 2H, $J = 7.2$ Hz); **19b** 0.13(s, 9H), 1.01(s, 3H), 1.10(s, 3H), 1.26(t, 3H, $J = 7.2$ Hz), 1.42(s, 9H), 1.48 and 2.08(AB quartet, 2H, $J = 13.7$ Hz), 1.58 and 2.34(AB quartet, 2H, $J = 13.4$ Hz), 1.81(s, 1H), 2.23 and 2.57(AB quartet, 2H, $J_{AB} = 15.3$ Hz), 4.0-4.2(ABX₃ system, 2H); ^{13}C -NMR, 75.4 MHz ($CDCl_3$) δ : **19a** 0.6, 14.3, 28.0, 30.6, 33.1, 33.6, 37.6, 38.0, 38.5, 50.9, 52.0, 59.7, 73.6, 79.8, 168.9, 172.0; **19b** 0.6, 14.4, 26.1, 28.0, 31.2, 40.2, 40.4, 40.6, 43.3, 44.0, 47.0, 59.5, 75.2, 80.3, 170.2, 171.6; Elemental analysis: calculated for $C_{20}H_{36}SiO_5$ C = 62.46%, H = 9.43%; found C = 62.59%, H = 9.51%.

Chlorothioanisole³²

A solution of thioanisole (42.65 g; 340 mmol) in CH_2Cl_2 (200 mL) was heated at reflux. Sulphuryl chloride (45.36 g, 340 mmol) in CH_2Cl_2 (75 mL) was added dropwise to this solution over a period of 90 min. The reflux was maintained for 4 h, the mixture was cooled to room temperature, and the solvent was removed in a rotatory evaporator. The residual orange oil was distilled under reduced pressure. Yield: 48.2 g (89%); b.p.: 66 - 69 °C / 0.15 mmHg.

Phenyl-(thiomethyl)-triphenylphosphonium chloride³³

Chlorothioanisole (36.0 g; 227 mmol) and NaI (1.02 g; 6.8 mmol; 0.05 equivalents) were added to a solution of

triphenylphosphine (65.6 g; 250 mmol) in acetonitrile (250 mL) and the mixture was refluxed for 24 h, and then cooled to room temperature. A white solid precipitated, which was filtered, washed with diethylether and recrystallized from CHCl_3 /ethyl acetate, giving a crystalline white solid. Yield: 72 g (75%); m.p.: 245-248 °C (lit³¹: 242-244 °C).

1-Phenylthio-vinyltriphenylphosphonium tetrafluoroborate (13)^{24a}

N,N-dimethylmethyleammonium iodide (Eschenmoser salt) (11.0 g; 64 mmol) was rapidly added to a solution of phenylthio-(methyl)-triphenylphosphonium chloride (12.6 g; 30 mmol) in dry acetonitrile (54 mL), and the mixture was refluxed under nitrogen for 15 h. Then the solvent was removed and CHCl_3 (100 mL) was added to the yellow solid. The solution was then washed with brine (3 x 10 mL). The organic phase was dried with MgSO_4 and the solvent was removed in a rotatory evaporator to give an orange oil. The addition of diethylether (50 mL) gave a yellow-orange solid, which was decanted and dissolved in boiling water. A yellow oil separated, which was decanted and the aqueous phase was treated with saturated solution of NaBF_4 . The product was extracted with CHCl_3 , filtered and concentrated. The addition of ethyl acetate gave the solid 1-phenyl-(thiovinyl)-triphenylphosphonium tetrafluoroborate (13). Yield: 10.2 g (70%); m.p.: 144-145 °C; $^1\text{H-NMR}$, 300 MHz (CDCl_3) δ : 6.3-6.6(m, 2H), 7.35-7.45(m, 5H), 7.75-7.90(m, 15H).

4- α -(β)-Carboethoxy-5- β -carbo-tert-butoxy-methyl-7,7-dimethyl-2-phenylthio-bicyclo-[3.3.0]-oct-1-ene (18)

A three-necked flask equipped with a reflux condenser and a dropping funnel was flame dried under a nitrogen flow. It was then allowed to reach room temperature and charged with KF (1.45 g; 25 mmol; 5 equivalents), 18-crown-6 (0.255 g) and dry acetonitrile (30 mL). The resulting suspension was then heated at reflux under nitrogen. To the heated suspension a solution of 19 (1.92 g; 5 mmol) and the phosphonium salt 13 (4.84 g; 10 mmol) in dry acetonitrile (45 mL) was added dropwise over a 90 min period. The reflux was maintained for 36-48 h, and then the solvent was evaporated and the residue was eluted through a silica gel column with hexane/ethyl acetate (9 : 1). The intermediate 18 was obtained as a mixture of diastereomers at the α -carboethoxy position, which was not separable. Yield: 2.10 g (95%). This compound was characterized as the methyl ester 27 after hydrolysis, separation of isomers and esterification with diazomethane.

Typical procedure for the reductions with DIBAL-H

A solution of DIBAL-H (0.65 mL; 0.65 mmol of a 1 M solution in toluene) was added dropwise to a solution of the diester 18 (0.13 g; 0.3 mmol) in CH_2Cl_2 (3 mL), at -78 °C.

After stirring the mixture for 2 h at -78 °C EtOH (0.5 mL), and then water (2-3 mL) was slowly added. The mixture was then stirred for a few minutes, treated with saturated aqueous NaHCO_3 , and extracted with CH_2Cl_2 (3 x 15 mL). TLC analysis showed several spots and the absence of the starting material. Analysis of the crude product by $^1\text{H-NMR}$ indicated the partial reduction of the tert-butyl ester and an absence of aldehyde protons. Attempts to separate the mixture by column chromatography were unsuccessful.

Attempts to epimerize 18

Sodium ethoxide (0.025 g; 0.036 mmol) was added to a solution of the diester 18 (0.15 g; 0.34 mmol) in EtOH (5 mL), and the mixture was stirred at room temperature for 20 h. The mixture was then cooled to room temperature and extracted with diethyl ether (3 x 15 mL). The organic phase was dried with MgSO_4 and filtered, and the solvent was evaporated. The crude product was analyzed and showed no change. The diester was then redissolved in EtOH (5 mL) and treated with sodium ethoxide (0.025 g; 0.036 mmol). The reflux was maintained for 3 days. A work up as above and analysis of the residue showed that no change in the isomeric ratio occurred.

4- α -(β)-Carboxy-5- β -carbo-tert-butoxy-methyl-7,7-dimethyl-2-phenylthio-bicyclo-[3.3.0]-oct-1-ene (26)

MeOH (10 mL) and a 10% aqueous NaOH solution (5 mL) were added to a solution of the diester 18 (0.430 g; 1 mmol) in THF (10 mL). The mixture was stirred at 60 °C (bath temperature) for 14 h and then cooled to room temperature, and the pH was adjusted to 6 with a 1 N HCl solution. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), dried with MgSO_4 and filtered, and the solvent was removed under vacuum. The residue was chromatographed in a silica gel column eluting with ethyl acetate. The two diastereomeric acids, 26a and 26b, were separated. Yield: 0.36 g (90%); m.p.: 26b 123-124 °C; 26a 87-89 °C; IR (cm^{-1}): 3144, 3073, 3059, 3041, 3004, 2954, 1717, 1706, 1439, 1367, 1231, 1147; mass spectrum (EI) m/z (rel intensity) 402(3.72), 346(24.02), 301(9.13), 287(71.35), 91(38.48), 57(100); $^1\text{H-NMR}$, 300 MHz (CDCl_3) δ : 26a 1.02(s, 3H), 1.17(s, 3H), 1.41(s, 9H), 1.70 and 1.90(AB system, 2H, J_{AB} = 14.2 Hz), 2.07(d, 1H, J = 14.6 Hz), 2.15(d, 1H, J = 14.6 Hz), 2.49 and 2.51(AB system, 2H, J_{AB} = 14.5 Hz), 2.50-2.60(m, 1H), 2.95-3.10(m, 2H), 7.17-7.31(m, 5H); 26b 0.98(s, 3H), 1.20(s, 3H), 1.49(s, 9H), 1.45 and 1.59 (AB system, 2H, J_{AB} = 16.9 Hz), 2.04(dd, 1H, J = 15.0, 2.3 Hz), 2.25(d, 1H, J = 15 Hz), 2.47 and 2.65(AB system, 2H, J_{AB} = 16.1 Hz), 2.70-2.80(m, 1H), 3.17(d, broad, 1H, J = 16.5 Hz), 3.29(dd, 1H, J = 8.3, 1.8 Hz), 7.19(dd, 1H, J = 7.2 Hz), 7.29(dd, 2H, J = 8.0, 7.2 Hz), 7.38(d, 2H, J = 8.0 Hz); $^{13}\text{C-NMR}$, 75.4 MHz (CDCl_3) δ : 26a 28.0, 30.7, 31.2, 39.7, 40.1, 40.4, 41.4, 50.9, 56.6, 59.6,

80.7, 122.7, 126.5, 128.9, 130.1, 134.2, 155.2, 170.9, 177.0. **26b** 28.1, 31.7, 31.9, 39.3, 39.5, 40.1, 45.3, 47.6, 49.9, 61.1, 82.6, 123.3, 126.4, 128.8, 129.9, 133.9, 152.3, 173.2, 175.2; Elemental analysis: calculated for $C_{23}H_{30}SO_4$ C = 68.62%, H = 7.51%; found C = 68.43%, H = 7.51%.

4- α -Carbomethoxy-5- β -carbo-tert-butoxy-methyl-7,7-dimethyl-2-phenylthio-bicyclo-[3.3.0]-oct-1-ene (27)

A solution of diazomethane in diethyl ether was added to a solution of **26a** (0.2 g; ~0.5 mmol) in dry diethyl ether (10 mL) at room temperature over a 15 min period. The resulting solution was magnetically stirred for 10 min and then the solvent was evaporated to give the diester **27a** as a colorless oil in a quantitative yield, which was recrystallized in cold from hexane. The diester **27b** was prepared in the same way. Yield: 0.21 g (quantitative); m.p.: **27a** 67–68 °C; IR (cm^{-1}): 2952, 2931, 2864, 1734, 1437, 1366, 1202, 1145, 1110; mass spectrum (EI) m/z (rel intensity) 416(3.79), 360(9.62), 301(59.02), 214(5.85), 131(14.23), 91(24.12), 57(100); ^1H -NMR, 300 MHz ($CDCl_3$) δ : **27a** 1.03(s, 3H), 1.16(s, 3H), 1.43(s, 9H), 1.73 and 1.91(AB system, 2H, J_{AB} = 14.2 Hz), 2.05(dd, 1H, J = 14.7, 3.8 Hz), 2.16(d, 1H, J = 14.7 Hz), 2.43 and 2.51(AB system, 2H, J_{AB} = 15.0 Hz), 2.55(d, 1H, J = 14.2 Hz), 2.95–3.10(m, 2H), 3.64(s, 3H), 7.16–7.31(m, 5H). **27b** 0.96(s, 3H), 1.21(s, 3H), 1.46(s, 9H), 1.31 and 1.69 (AB system, 2H, J_{AB} = 14.0 Hz), 2.05(td, 1H, J = 15.0, 2.1, 2.0 Hz), 2.22(d, 1H, J = 15.0 Hz), 2.38 and 2.42(AB system, 2H, J_{AB} = 13.5 Hz), 2.69–2.78(m, 1H), 2.96(dd, 1H, J = 16.0, 1.5 Hz), 3.45(dd, 1H, J = 7.6, 1.5 Hz), 3.66(s, 3H), 7.18(dd, 1H, J = 7.3 Hz), 7.30(dd, 2H, J = 8.0, 7.3 Hz), 7.43(d, 2H, J = 8.0 Hz); ^{13}C -NMR, 75.4 MHz ($CDCl_3$) δ : **27a** 28.0, 30.7, 31.0, 39.0, 39.7, 40.2, 41.4, 50.7, 51.4, 56.4, 59.5, 80.3, 122.6, 126.4, 128.8, 130.0, 134.5, 155.4, 170.7, 172.8. **27b** 29.0, 32.5, 32.6, 40.7, 41.1, 41.7, 46.7, 47.8, 50.2, 52.0, 63.5, 81.4, 123.4, 127.5, 130.1, 130.9, 135.9, 155.8, 171.0, 175.2; Elemental analysis: calculated for $C_{24}H_{32}SO_4$ C = 69.19%, H = 7.74%; found C = 69.02%, H = 7.76%.

4- β -Hydroxymethyl-5- β -carbo-tert-butoxy-methyl-7,7-dimethyl-2-phenylthio-bicyclo-[3.3.0]-oct-1-ene (28)³⁴

Et_3N (1.25 mL; 9 mmol) was added to a solution of the carboxylic acid **26a** (2.80 g; 7 mmol) in dry THF (25 mL) at room temperature. The mixture was cooled to -5 °C and then $ClCO_2Et$ (0.86 mL; 9 mmol) was added dropwise for 5 min. The resulting mixture was stirred for 45 min at -5 °C and a white precipitate gradually formed. The precipitate was removed by filtration. The filtrate was slowly added (10 min) to a solution of $NaBH_4$ (0.95 g; 25 mmol) in water (20 mL) at 0 °C. Then the mixture was stirred for 15 min at 0 °C. The ice bath was removed and the mixture was stirred at room temperature for 12 h. 1 N HCl was added until pH 6 and the reaction was extracted with CH_2Cl_2 . The

organic phase was dried with $MgSO_4$, the solvent was removed in a rotatory evaporator and the residue was used without further purification in the next step. IR (cm^{-1}): 3438, 3430, 3428, 2950, 2929, 1718, 1476, 1366, 1253, 1151, 1024; mass spectrum (EI) m/z (rel intensity) 388(9.87), 358(2.40), 332(22.56), 315(9.00), 301(51.82), 273(100), 177(38.82), 91(38.23), 57(72.54); ^1H -NMR, 300 MHz ($CDCl_3$) δ : 1.04(s, 3H), 1.17(s, 3H), 1.47(s, 9H), 1.72 and 1.82(AB system, 2H, J_{AB} = 14.2 Hz), 2.00 and 2.16(AB system, 2H, J_{AB} = 14.9 Hz), 2.30 and 2.50(AB system, 2H, J_{AB} = 16.3 Hz) 2.30–2.50(m, 2H), 3.60(ABX, 2H, J_{AB} = 12.2 Hz, J_{BX} = 9.5 Hz, J_{AX} = 4.0 Hz), 7.15–7.30(m, 5H); ^{13}C -NMR, 75.4 MHz (acetone d_6 : $CDCl_3$, 4 : 1) δ : 26.6, 29.4, 29.9, 38.0, 38.8, 39.2, 40.2, 50.1, 55.3, 57.5, 60.4, 79.0, 121.3, 125.1, 127.8, 128.3, 134.2, 157.9, 171.0; HRMS calculated: 388.2072, obtained: 388.2074.

Octahydro-8,8-dimethyl-2-oxo-pentalene-[1,6a-c]-pirane-6-one (17)^{24a}

The alcohol **28**, prepared as described in the previous procedure, was dissolved in $CHCl_3$ (20 mL), without further purification, and trifluoroacetic acid (5 mL) was added to this solution. The resulting pink solution was refluxed for 48 h and then cooled to room temperature. Saturated aqueous $NaHCO_3$ was slowly added until pH 7. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried with $MgSO_4$, filtered and evaporated under vacuum to give a solid product, which was purified by washing with hexane or chromatographed in a silica gel column [hexane : ethyl acetate (2 : 1)]. Yield: 0.70 g (45% from **26a**); m.p.: 108–109 °C; IR (cm^{-1}): 2952, 2931, 2855, 1745, 1738, 1727, 1308, 1291, 1260, 1227, 1079; mass spectrum (EI) m/z (rel intensity) 222(11.13), 180(54.83), 165(9.61), 122(18.33), 107(31.42), 95(48.20), 41(100); ^1H -NMR, 300 MHz ($CDCl_3$) δ : 0.90(s, 3H), 1.07(s, 3H), 1.71(d, 1H, J = 13.1 Hz), 1.79(dd, 1H, J = 13.1 and 1.1 Hz), 1.83(d, 1H, J = 13.1 Hz), 1.90(ddd, 1H, J = 13.1, 4.2, 1.1 Hz), 2.44(ddd, 1H, J = 18.0, 7.9, 1.9 Hz), 2.59 and 2.67(AB system, 2H, J_{AB} = 15.0 Hz), 2.50–2.62(m, 2H), 2.75(dd, 1H, J = 18.0, 9.0 Hz), 4.11(dd, 1H, J = 11.9, 5.3 Hz), 4.44(dd, 1H, J = 11.9, 4.2 Hz); ^{13}C -NMR, 75.4 MHz ($CDCl_3$) δ : 28.4, 29.1, 40.8, 41.1, 41.3, 42.4, 44.7, 49.5, 57.8, 60.0, 69.2, 171.7, 217.1; Elemental analysis: calculated for $C_{13}H_{18}O_3$ C = 70.24%, H = 8.16%; found C = 70.06%, H = 8.24%.

Attempted acylation of 17 with LDA-dimethylcarbonate

A solution of LDA (0.055 mol) was prepared in the usual way and cooled to -78 °C, and this solution was added dropwise to the ketolactone **17** (0.011 g; 0.05 mmol) in THF (1 mL). After 30 min $CO(OMe)_2$ was added at -78 °C and the reaction was allowed to reach room temperature (3 h). Saturated aqueous $NaHCO_3$ (10 mL) was added and

the mixture extracted with CH_2Cl_2 (3 x 15 mL). The organic phase was dried with MgSO_4 and filtered, and the solvent was removed in a rotatory evaporator. Analysis of the residue showed only unchanged ketolactone **17**.

Reaction of the ketolactone 17 with methylmagnesium carbonate and diazomethane

The ketolactone **17** (10 mg) was placed in a 10 mL flask. Then, 1 mL of a 3 M solution of methylmagnesium carbonate in DMF was added by syringe under nitrogen, and the resulting mixture was slowly treated with a mixture of ice-cooled concentrated HCl (1 mL) and diethylether (10 mL). The phases were separated and the organic phase was extracted with diethylether (2 x 10 mL). The organic phase was washed with brine, dried with MgSO_4 and filtered, and the solvent was evaporated in a rotatory evaporator. The residue was dissolved in dry diethyl ether, cooled to 0 °C, and treated with an excess of a diazomethane solution in diethyl ether. After removal of the excess of diazomethane and the solvent the product **35** was obtained as a colorless oil. Yield: 7 mg (60%). This intermediate was characterized by its mass and ^1H -NMR spectra. Mass spectrum (EI) m/z (rel intensity): 294(31.2), 279(1.55), 263(19.17), 236(77.91), 222(60.43), 205(24.91), 166(100); ^1H -NMR, 300 MHz (CDCl_3) δ : (ABX system, 2H), (A proton: 1.56-1.61, $J_{\text{AB}} = 12.9$ Hz, $J_{\text{AX}} = 6.6$ Hz; B proton: 1.97-2.01, $J_{\text{AB}} = 12.9$ Hz, $J_{\text{BX}} = 9.3$ Hz), 1.76(s broad, 2H), 2.56-2.62(AB system, $J_{\text{AB}} = 14.3$ Hz, 2H), 3.12-3.17(m, 2H), 3.72(s, 3H), 3.85(s, 3H), ABX system, 2H (A proton: 4.32-4.35, $J_{\text{AB}} = 11.7$ Hz, $J_{\text{AX}} = 5.2$ Hz; B proton: 4.46-4.49, $J_{\text{AB}} = 11.7$ Hz, $J_{\text{BX}} = 4.3$ Hz).

*1,2,4,4a,6a,7,8,9-Octahydro-8,8-dimethyl-6-pyrrolidin-2-oxopentalene-[1,6a-e]-pirane-5-methyl-carboxylate (29)*²⁷

The ketolactone **17** (0.033 g; 0.15 mmol), dry benzene (3 mL), pyrrolidine (0.030 mL; 0.4 mmol) and a crystal of p-toluenesulphonic acid were placed in a flask equipped with a reflux condenser and a Dean-Stark apparatus. The mixture was refluxed for 6h and then the solvent was evaporated and the excess pyrrolidine was removed under high vacuum. The resulting solid was dissolved in dry benzene (3 mL) and treated with ClCO_2Me (0.035 mL; 3 equivalents). After 10 h and 20 h under reflux two more portions of ClCO_2Me (0.035 mL) were added. The mixture was refluxed until complete reaction, cooled to room temperature, and slowly treated with 10% aqueous HCl (1 mL) and water (2 mL), stirred for 15 min at room temperature and extracted with CH_2Cl_2 /ether (50 mL). The aqueous phase was treated with more 10% aqueous HCl (1 mL) and then extracted with CH_2Cl_2 (10 mL). The combined organic phases were washed with brine, dried with MgSO_4 , and the solvent was evaporated. The residual oil was purified by column chromatography in silica gel eluting with

hexane : ethyl acetate (1 : 3). Yield: 47 mg (94%); IR (cm^{-1}): 2950, 1748, 1680, 1560, 1446, 1249, 1216, 1123, 1068; mass spectrum (EI) m/z (rel intensity) 333(50.96), 318(15.94), 302(26.48), 274(100), 260(22.76), 218(23), 204(14.72), 70(63.92); ^1H -NMR, 300 MHz (CDCl_3) δ : 1.06(s, 6H), 1.48(dd, 1H, $J = 12.6, 8.4$ Hz), 1.74 and 1.78(AB system, 2H, $J_{\text{AB}} = 13.4$ Hz), 1.75-2.00(m, 4H), 2.04(ddd, 1H, $J = 12.6, 8.4, 1.2$ Hz), 2.55 and 2.59(AB system, 2H, $J_{\text{AB}} = 14.3$ Hz), 3.07(dd, 1H, $J = 8.4, 8.4$ Hz), 3.17(t, 1H, $J = 5.6$ Hz), 3.10-3.30(m, 2H), 3.63(s, 3H), 3.55-3.70(m, 2H), 4.13(dd, 1H, $J = 11.4, 6.4$ Hz), 4.53(dd, 1H, $J = 11.4, 4.8$ Hz); ^{13}C -NMR, 75.4 MHz (CDCl_3) δ : 25.2, 28.6, 29.2, 40.6, 42.5, 47.6, 49.1, 50.1, 51.9, 52.8, 56.6, 58.8, 71.2, 89.3, 163.5, 165.1, 173.0; HRMs calculated for $\text{C}_{19}\text{H}_{27}\text{NO}_4$: 333.1940, found 333.1942.

*Reduction of 29 with sodium cyanoborohydride*²⁸

A crystal of bromocresol green and NaBH_3CN (0.026 g; 0.41 mmol; 3 equivalents) was added to a solution of the enamine **29** (0.046 g; 0.138 mmol) in MeOH (3 mL) at room temperature. 2 N aqueous HCl in MeOH was added to this solution dropwise in order to maintain the yellow color of the mixture, which was stirred at room temperature for 12 h. Then more NaBH_3CN (8 mg; 1 equivalent) was added and the mixture was stirred for an additional period of 2 h, and HCl / MeOH was added as required to maintain the yellow color. The pH was adjusted to 7 with saturated aqueous NaHCO_3 , and the mixture was extracted with CH_2Cl_2 (2 x 10 mL) and ether (2 x 10 mL). The organic phase was washed with brine and dried with MgSO_4 . The solvent was evaporated and the residue used in the next step without further purification.

1,2,4,4a,6a,7,8,9-Octahydro-8,8-dimethyl-2-oxopentalene-[1,6a-c]-pirane-5-methyl-carboxylate (30)

The product **40** obtained in the preceding step was dissolved without purification in CH_2Cl_2 (3 mL), treated with m-chloroperoxybenzoic acid (0.033 g; 0.151 mmol, 1.1 equivalents; 85%) and the mixture was stirred at room temperature for 2 h. Then the solvent was evaporated, giving a white solid, which was dissolved in dry THF (3 mL) and then treated with anhydrous K_2CO_3 (1 g). The mixture was stirred at room temperature for 12 h. Then water (15 mL) was added to the mixture and the aqueous phase was extracted with CH_2Cl_2 (20 mL) / diethyl ether (20 mL). The combined organic phases were washed with brine, dried with MgSO_4 , the solvent was evaporated, and the residue was chromatographed in silica gel [hexane : ethyl acetate (1 : 3)]. Yield: 21.1 mg (60%); IR (cm^{-1}): 2952, 2927, 1752, 1713, 1633, 1436, 1254, 1218, 1114, 1081; mass spectrum (EI) m/z (rel intensity) 264(7.85), 249(2.07), 232(25.89), 205(38.67), 192(89.16), 136(76.72), 105(47.04), 41(100); ^1H -NMR, 300 MHz

(CDCl₃) δ : 1.02(s, 3H), 1.06(s, 3H), 1.37(dd, 1H, $J = 13.0$, 5.9 Hz), 1.71 and 1.77(AB system, 2H, $J_{AB} = 13.5$ Hz), 1.86(dd, 1H, $J = 13.0$, 9.4 Hz), 2.56 and 2.64(AB system, 2H, $J_{AB} = 14.5$ Hz), 2.90-3.25(m, 2H), 3.72(s, 3H), 4.48 and 4.52(A), 4.42 and 4.46(B) (ABX system, 2H, $J_{AB} = 11.8$ Hz, $J_{AX} = J_{BX} = 4.1$ Hz), 6.80-6.90(m, 1H); ¹³C-NMR, 75.4 MHz (CDCl₃) δ : 29.1, 29.5, 40.7, 42.1, 46.0, 51.5, 51.9, 53.6, 56.5, 58.2, 67.7, 131.7, 149.9, 164.4, 172.1; HRMs calculated for C₁₅H₂₀O₄: 264.1361, found 264.1369.

Pentalenolactone E methyl ester (16)^{13a}

The lactone **30** (16.0 mg; 0.1 mmol) was dissolved in magnesium methyl carbonate (MMC) (3 mL; 2M solution in DMF) and heated at 150 °C for 3 h. Then the mixture was cooled and added to an Erlenmeyer containing ice, HCl and diethyl ether. The mixture was extracted with diethyl ether (3 x 20 mL), dried with MgSO₄ and the solvent was

evaporated. The residue was dissolved in 1 mL of a solution of NaOAc (105 mg), AcOH (4 mL), formaline (2.92 mL) and Et₂NH (1.0 mL), and heated at 100 °C for 5 min. The mixture was cooled to room temperature, added to water and extracted with diethyl ether (3 x 15 mL). The organic phase was dried with MgSO₄, and the solvent was evaporated. The residual oil was purified by column chromatography in silica gel. Yield: 7.5 mg (43%); IR (cm⁻¹): 3397, 2952, 2928, 1739, 1716, 1635, 1260, 1133, 1107; ¹H-NMR, 300 MHz (CDCl₃) δ : 1.05(s, 3H), 1.06(s, 3H), 1.44(dd, 1H, $J = 13.0$, 5.9 Hz), 1.74(d, 1H, $J = 13.9$ Hz), 2.15(dd, 1H, $J = 13.9$, 0.9 Hz), 1.89(ddd, 1H, $J = 13.0$, 9.0, 0.9 Hz), 3.2-3.3(m, 1H), 3.30-3.35(m, 1H), 3.75(s, 3H), 4.27 and 4.31 / 4.32 and 4.35(ABX system, 2H, $J_{AB} = 11.4$ Hz, $J_{AX} = 4.7$ Hz), 5.56(s, 1H), 5.91(s, 1H), 6.84-6.86(m, 1H); ¹³C-NMR, 90.4 MHz (CDCl₃) δ : 29.6, 29.7, 40.7, 46.4, 51.6, 53.5, 55.2, 57.0, 58.1, 67.4, 120.0, 131.1, 144.6, 150.0, 164.4, 170.1.

Scheme 5.

Results and Discussion

Following the general strategy described in Scheme 4, the synthesis of pentalenolactone E methyl ester (**16**) was accomplished in 13 steps¹⁴, as shown in Scheme 5.

The starting material, **21**, was prepared in three steps from isobutyraldehyde and allyl alcohol, as shown in Scheme 6¹⁶.

The first step consisted of the condensation of isobutyraldehyde with allyl alcohol catalyzed by p-toluenesulphonic acid (PTSA) in p-cymene. After purification, the product (**31**) was obtained in a 90% yield. **31** was transformed into **32** by means of oxidation of the double bond, using catalytic amounts of palladium (II) chloride in the presence of an excess of copper (II) chloride and oxygen. Finally, **32** was transformed into **21** with an 80% yield by means of an intramolecular aldol condensation, by refluxing **32** for 48 h in the presence of aqueous 5% KOH in a mixture of THF/diethyl ether.

The silyl ether **22** was obtained by reacting a mixture of **21** and triethylsilyl hydride in dry benzene, previously purged for 1 h at 0 °C with dry Argon, with tris-(triphenylphosphine)-rhodium chloride (catalytic) for 3-4 h at 70 °C¹⁷. After filtration through a pad of Florisyl and distillation, **22** was obtained in an 80% yield. The cyclopropanation of **22** was achieved by the slow addition of tert-butyl diazoacetate in dry benzene in the presence of copper sulphate (catalytic) in benzene¹⁵. The reaction was performed at 90 °C (bath temperature) and the diazo-compound was added within 1 h. The product was obtained in an 80% yield. By increasing the addition time to 4 h no difference in yield was observed. However, by performing the reaction at a 100 mmol scale and increasing the addition time to 10 h a 93% yield of the cyclopropane **23** was obtained as a mixture of diastereomers in a 1.2 : 1.0 *cis/trans* ratio, which was used directly in the next step. Treatment of the isomeric mixture of **23** with triethylamine/hydrofluoric acid in THF at room temperature for 4 h led to the ketoester **24** in an 86% yield after column chromatography in silica gel. The first attempt to transform **20** into the silylenolether **24** was made by heating **20** with trimethylsilyltriflate (TMSOTf)¹⁸. This is an efficient reagent for preparing silylenolethers at low temperatures, leading to the preferential formation of the thermodynamic product¹⁸.

Following this procedure, **20** was reacted with TMSOTf and triethylamine in carbon tetrachloride at 0 °C, and then the system was allowed to reach room temperature. Although ¹H-NMR analysis of the reaction mixture showed the formation of the silylenolether **24**, the main product resulted from the hydrolysis of the t-butylester group. In view of this result we decided to use trimethylsilylchloride and triethylamine in DMF as the silylating system¹⁹, heating the mixture to 135 °C. At higher temperatures, silylenolether **24** decomposed, while at lower temperatures the ketoester **20** did not react to an appreciable extent. The reaction time was an important factor, and to avoid decomposition of **24** it can not exceed 4 h. As expected¹⁹, this method led to a mixture of (**24**) and (**25**) in an 87 : 13 ratio in a 75% yield. The separation of the mixture proved to be difficult. All attempts to separate the isomers on a large scale by column chromatography in silica gel led to the decomposition of the silylenolether **24**. It was more convenient to directly use the mixture and perform the separation later, when products with a greater difference in polarity are formed. The silylenolether **24** was transformed into the cyclopropane **19** by using a procedure similar to that used to transform **22** into **23**¹⁵. The first attempt to transform **24** into **19** was made using 2 equivalents of ethyldiazoacetate and a reaction time of 2-3 h. Under these conditions the yield was *ca.* 40%. By increasing the reaction time to 6 h and using a larger excess of ethyldiazoacetate (4 equivalents) the yield was increased to 85%. As in the transformation of **22** into **23**, a mixture of diastereomers was formed, which was used without separation in the next step. Analytically pure samples of **19a** and **19b** were obtained by column chromatography in silica gel. At this stage it was possible to separate **19a** and **19b** by column chromatography. With the cyclopropane **19** in hand we were able to perform the key step of the synthesis. The experimental procedure was similar to one previously described¹⁵. Reflux of **19** in acetonitrile with a mixture of KF, 18-crown-6 and the vinylphosphonium salt **13** for 36-48h gave the [3+2] addition product **18** in a 95% yield after column chromatography. As expected, a mixture of diastereomers at C₄ was obtained in a 1 : 1 (*anti* : *syn*) ratio. Since only the *syn* isomer **18a** gives the desired lactone **17**, attempts were made to epimerize the C₄ center. Sodium

Scheme 6.

ethoxide in ethanol at room temperature and at reflux were used without success. Even maintaining the mixture under reflux for several days or using other systems such as DBU/THF did not change the isomeric ratio. Attempts to separate **18a** from **18b** by column chromatography were also unsuccessful. It was possible in a posterior step to enrich the mixture with the *syn* isomer of the carboxylic acid **26** derived from **18**, and to separate the *syn* **26a** from the *anti* **26b** isomer. The next step in our synthetic plan was the construction of the lactone ring, leading to the intermediate **17**. To accomplish this, a selective reduction of the ethylester group of **18** in the presence of the tert-butyl group was necessary. The reagent chosen to perform this transformation was DIBAL-H, since it selectively reduces ethyl esters in the presence of tert-butylesters²⁰. All attempts to transform **18** directly into **28** were unsuccessful. In view of this, we resolved to selectively hydrolyze the ethyl ester **18** to the corresponding carboxylic acid **26**. This transformation was accomplished by reacting **18** in THF/MeOH with a 5% aqueous solution of KOH. Initially, the reaction performed at room temperature and monitored by TLC was very slow. The mixture was heated to 60 °C, and after 6 h all starting material was consumed. Neutralization of the mixture with ammonium chloride or with diluted (1 N) hydrochloric acid, followed by extraction and purification by column chromatography, gave the carboxylic acid **26** in a 90% yield. As anticipated, at the carboxylic acid stage the separation of the diastereomers **26a** and **26b** was successful and, surprisingly, the mixture was enriched in the desired *syn* isomer **26a**. Actually, the hydrolysis of a 1 : 1 mixture of **18a** and **18b** gave a 1.5 : 1 mixture of **26a** and **26b**, respectively. With the pure acids **26a** and **26b** in hand, we decided to transform them into the corresponding methyl esters **27a** and **27b** to permit a more detailed ¹H-NMR analysis.

The methyl esters **27a** and **27b** were obtained in quantitative yields by treatment of an ether solution of the corresponding carboxylic acids **26a** and **26b** with diazomethane. With the pure esters **27a** and **27b** available, we attempted the epimerization of pure **27b** by refluxing with a catalytic amount of sodium methoxide in methanol for 4 days. After this period, ¹H-NMR analysis of the reaction mixture showed a 2 : 1 ratio of **27b** to **27a**. Attempts to change this ratio by further refluxing for several days were unsuccessful. With the two diastereomeric acids **26a** and **26b** separated, the transformation of **26a** into **28** was performed. Several procedures are available to selectively transform a carboxylic acid into an alcohol in the presence of a tert-butyl ester. Our first approach was to use catechol borane as the reducing agent²¹. However, this method was not efficient in this case, since the main product was the catechol ester derived from **26a**. Use of N-ethyl-5-phenylisoxazol-3'-sulphonate (NEPIS) following the described method²² did not give the expected alcohol **28**. A

two step procedure was then adopted, which consisted of the transformation of the carboxylic acid **26a** into the corresponding acid chloride, followed by reduction with sodium borohydride²³. By reacting **26a** with Ph₃P/CCl₄^{23a} the corresponding acid chloride was formed, which was then reduced to the alcohol, although in a very low yield. In view of these results, we decided to try the reduction of a mixed anhydride of the acid. For this purpose, the acid was treated with methyl chloroformate/Et₃N, and the crude product was treated with NaBH₄ at room temperature, giving the alcohol **28**, which was essentially pure by ¹H-NMR analysis, and which was used in the lactonization step without further purification. The lactonization and the hydrolysis of the vinyl sulphide of the intermediate **28** were performed in a single step by refluxing **28** with trifluoroacetic acid (TFA) in chloroform²⁴ for 3 days, leading to the ketolactone **17**. The lactonization step occurred rapidly in the presence of TFA; however, the hydrolysis of the vinyl sulphide required heating under reflux for 3 days. The mixture was neutralized, extracted and chromatographed on a silica gel column. This sequence allowed the isolation of the desired ketolactone **17** in a 60% overall yield, starting from **26a**.

The path from the ketolactone **17** to pentalenelactone E methyl ester (**16**) seemed quite straightforward at this stage, *i.e.* it should involve the introduction of a carbomethoxy group at the α position of the keto group, the removal of the ketone with the formation of the double carbon-carbon bond, and a final introduction of the methylene group. Deprotonation of the ketone with LDA at -78 °C to generate the enolate was attempted, followed by treatment with ClCO₂Me or (MeO)₂CO to give **33** (Scheme 7), but only the starting material was recovered. The use of the larger amounts of the base, the increase in the reaction time, the use of different bases such as NaH and t-BuOK, and of (EtO)₂P(O)CO₂Me as the carbomethoxylation reagent²⁵, were also unsuccessful. Heating the reaction mixture at 80 °C furnished O-acylation products. Additional experiments employing methylmagnesium carbamate (MMC), a useful reagent for the α-carboxylation of ketones, lactones and nitriles²⁶, gave a mixture of unidentified products. The addition of MeOH/HCl or diazomethane to the reaction mixture (to convert the expected unstable α-ketoacid **34** into the more stable α-ketoester **33**) gave small amounts of the desired carbomethoxylation product **33**, which was accompanied, however, by the methylvinylether **35** as the main product in *c.a.* a 60% yield. Attempts to hydrolyze the enol ether **35** to the corresponding ketone **33**, and to reduce the double bond with H₂/Pd were fruitless, the starting materials being recovered unchanged. The crude product **34** was treated with NaBH₄ under several conditions, with the expectation that the β-hydroxyacid would not be decarboxylated and therefore easily converted into the corresponding methyl ether by treatment with diazomethane.

Scheme 7.

Scheme 8.

This attempt was also unsuccessful, giving only a mixture of unidentified products.

In view of the disappointing results obtained with the direct carbomethoxylation of the ketolactone **17**, we de-

cided to use the enamine derivatives **37** or **39** (Scheme 8) to achieve this goal. Several procedures were tried to optimize the desired conversion²⁷. Reaction of the ketolactone **17** with morpholine under PTSA catalysis furnished the enamine **37** as the only product identified by MS and ¹H-NMR analysis. This enamine was treated *in situ* with methyl chloroformate under reflux, and hydrolyzed in sequence with 10% HCl at room temperature. Spectral analysis revealed the presence of the carboethoxy group, but only incomplete hydrolysis of **38** to **33**. Consequently, the yield was only moderate, in agreement with Stork²⁷ who reported a maximum yield of 50% for the reaction of enamines with ethylchloroformate, due to the consumption of half of the enamine by the hydrochloric acid formed during the reaction. The same author reported the uselessness of the addition of a tertiary amine in these acylations. Use of pyrrolidine instead of morpholine, and the addition of an amine (Et₃N or PhNEt₂) at the condensation step, resulted in the recovery of the starting **17** after the hydrolysis step. The pyrrolidine enamine (**39**) route was then reinvestigated, taking care to carefully eliminate all the excess pyrrolidine after the enamine **39** formation. A small excess of methylchloroformate was added in intervals during the acylation step. Following this procedure, the enamine ester **29** was obtained in a 93% yield. Since we found strong resistance of **38** to hydrolysis, we directed our efforts to substitute the hydrolysis step for a carbon-carbon double bond reduction-pyrrolidine elimination sequence and directly obtain compound **30**. To achieve this goal the enamine ester **29** was treated with NaBH₃CN in aqueous HCl at room temperature, and was cleanly converted to the saturated amine **40**²⁸. Product **40** was oxidized with MCPBA to the corresponding amine oxide²⁹. After 2 h, when no more starting material was detected by TLC, the isolated product was directly treated in THF with K₂CO₃. The unsaturated ester-lactone **30** was isolated in its pure form after silica gel column chromatography with a 60% yield.

Since the final α -methylenation of the lactone **30** had been previously reported by Paquette^{13a}, our formal synthesis was complete. Nevertheless, the methylenation was performed in accordance with the described procedure by means of the reaction of **30** with methylmagnesium carbonate (MMC) in DMF at 150 °C for 3 h, followed by acidification with diluted HCl and heating at 100 °C for 5 min with a mixture of NaOAc, HOAc, formalin and Et₂NH. After chromatographic purification, Pentalenolactone E methyl ester was isolated in a 43% yield. The spectroscopic data of the final product were in full agreement with the literature⁹.

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