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ENANTIOMERIC β-ANGELICA LACTONE EPOXIDES: THEIR SYNTHESES FROM SUITABLE CHIRAL PRECURSORS AND THEIR USE IN THE PREPARATION OF BLASTMYCINONE

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Summary.- Syntheses of (S)-β-angelica lactone from L-tartaric acid and (R)-γ-hydroxymethyl-γ-butyrolactone, 5, are reported. Alternative routes to prepare 5 from S- and R-glutamic acids and D-ribonolactone, respectively, are also presented. Epoxides derived from (R)- and (S)-β-angelica lactones have been obtained and their use in the synthesis of both (+)- and (-)-blastmycinone, 24, has been established.

INTRODUCTION

The use of simple natural products as chiral precursors in the synthesis of optically active compounds has been widely applied in the last ten years.[1] In this way, following our studies on the preparation of interesting γ-lactonic substances,[2] we have investigated synthetic routes to accede to both enantiomers (-)-(R)- and (+)-(S)-β-angelica lactones, (-)-1 and (+)-1 respectively, and to some derivatives that could be employed as useful precursors in enantioselective synthesis. The differently substituted γ-valerolactone moiety is present in the structure of several natural products[3] and in these cases, regio- and stereocontrolled functionalization at the and carbon atoms of the lactone are extremely important. Within this class of substances many products having an α-alkyl-β-hydroxy-γ-methylbutyrolactone-type constitution are found. Therefore, the epoxy derivatives (+)-2 and (-)-2 seemed to be suitable intermediates to accomplish the synthesis of this kind of compounds, such as blastmycinone,[4] litsenolides,[5] and some lipid metabolites from the coral Plexaura Flava.[6]

(-)-(R)-β-angelica lactone, (-)-1, has been prepared for the first time in our laboratory,[7] and later by Joullié and Chen,[8] from D-ribonolactone, 3. In this paper, we report the synthesis of (+)-(S)-β-angelica lactone, (+)-1, from two different chiral precursors: L-tartaric acid, 4, and (R)-(-)-γ-hydroxymethyl-γ-butyrolactone, 5. We also present here the preparation of the two new epoxides (+)-2 and (-)-2, as well as their use in the synthesis of blastmycinones.

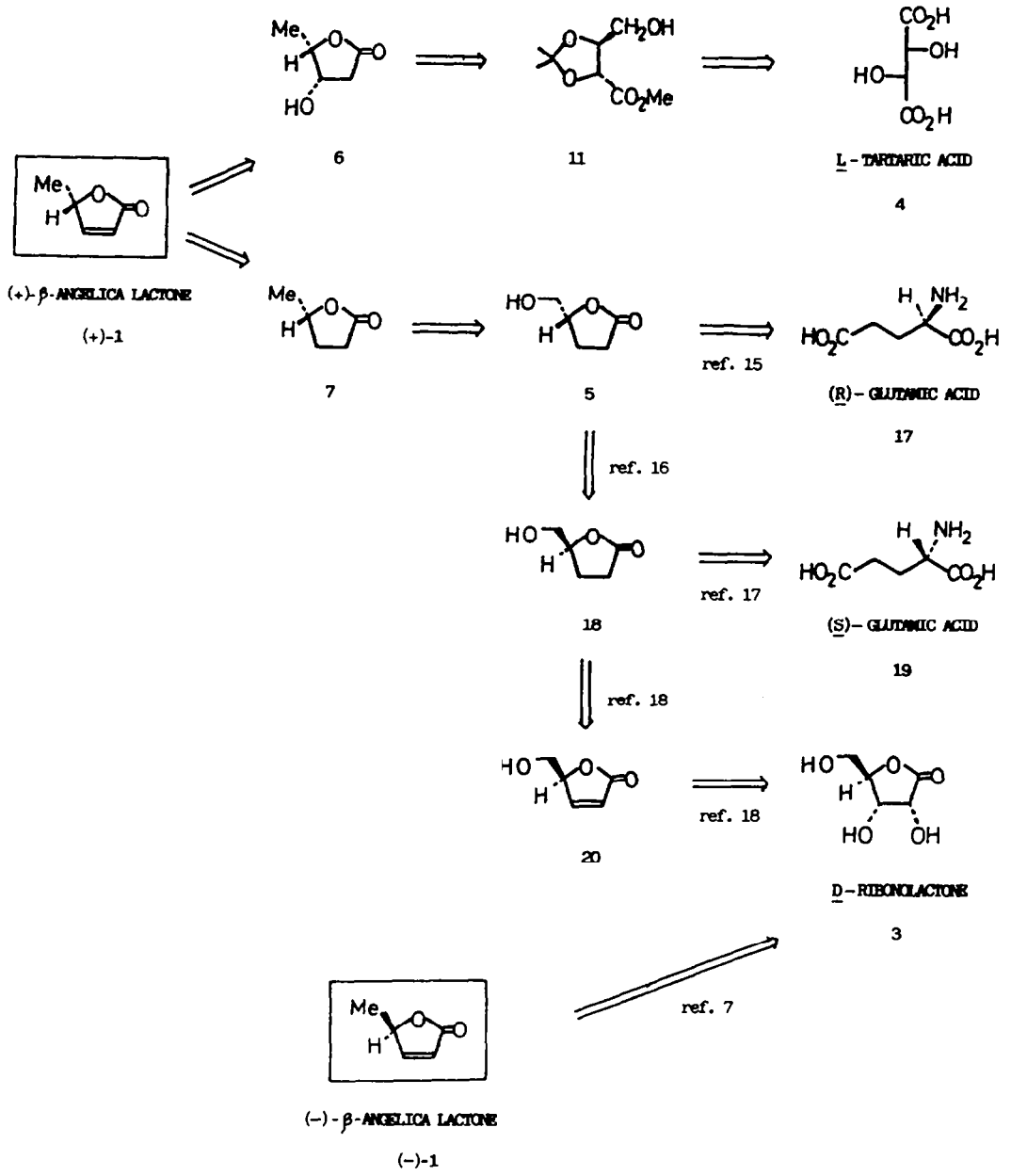
RESULTS AND DISCUSSION

1. (+)-(S)-β-angelica lactone, (+)-1

Inspection of the retrosynthetic pathway shown in Scheme 1 for compound (+)-1 reveals two key intermediates: 2,5-dideoxy-L-xylono-γ-lactone, 6, and (S)-γ-valerolactone, 7, creation of the double bond involving an elimination process in both routes.

Hydroxylactone 6 was easily prepared from the cheap and readily available L-tartaric acid,[9] 4, following the sequence depicted in Scheme 2. A crucial intermediate is the hydroxyester 11 in which the oxidation level of the end-chain carbon atoms has been differentiated.

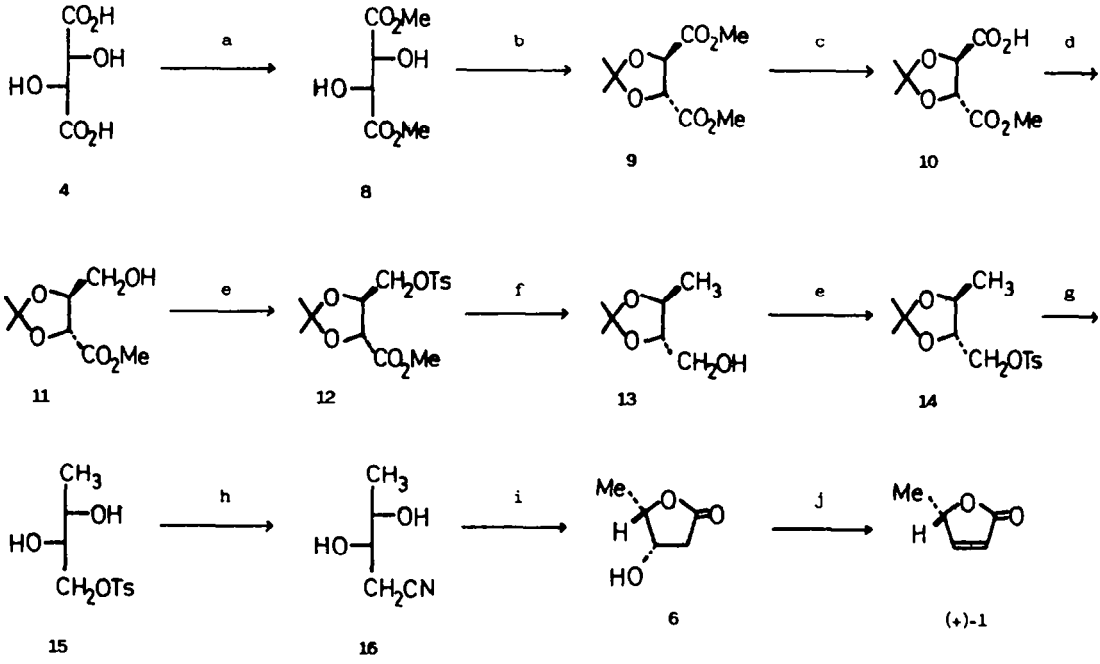
Monosaponification of the diester acetonide 9, using one mol of methanolic KOH, gave 10 in 48 % yield.[10] The carboxyl group was chemoselectively reduced upon the action of the complex BH_3-THF[11] (0.4 M in THF) at 0° for 8 hours affording 11 in 58 % yield.[10,12] In this reaction, the use of reducing agent solutions in concentrations higher than 1.5 M was not compatible with the presence of the ketal protecting group, giving 11 in low yields along with by-products resulting from molecular rearrangements. Tosylation of 11 and subsequent reduction with $LiAlH_4$ gave the alcohol 13. At this stage, transformation of one of the two equivalent carboxyl groups in the L-tartaric acid molecule into a methyl group had been achieved.



Scheme 1

Tosylation of 13 followed by acid methanolysis of the ketal gave the new dihydroxytosyl derivative 15, m.p. 82-83°, $[\alpha]_D^{20}$ =-1.97° (c=0.4, $CHCl_3$). The carbon chain was then extended by

reaction with sodium cyanide in DMSO, affording the nitrile **16** as a viscous oil, $[\alpha]_D^{20}$ = -0.66° (c=2.1, $CHCl_3$). Deprotection of the glycol was carried out before the displacement of the tosyloxy group by cyanide ion to prevent the steric hindrance of the gem-dimethyl substitution in the dioxolane ring, that would difficult the attack of the nucleophile.[13] Treatment of **16** with methanolic hydrogen chloride afforded the hydroxylactone **6**, which was then reacted with 1.2 moles of mesyl chloride and 2 moles of triethylamine in CH_2Cl_2 as solvent.[14] Elimination of methanesulfonic acid from the mesylate formed in situ led to quantitative formation of (+)-(S)- -angelica lactone, **(+)-1**, as a liquid, b.p. 98-100° (oven)/15 torr, $[\alpha]_D^{20}$ = +93.8° (c = 0.5, $CHCl_3$).(Lit[7] $[\alpha]_D^{20}$ = -95.9° (c = 0.7, $CHCl_3$) for the enantiomer). The overall yield of (+)-1 from L-tartaric acid was 10 %.

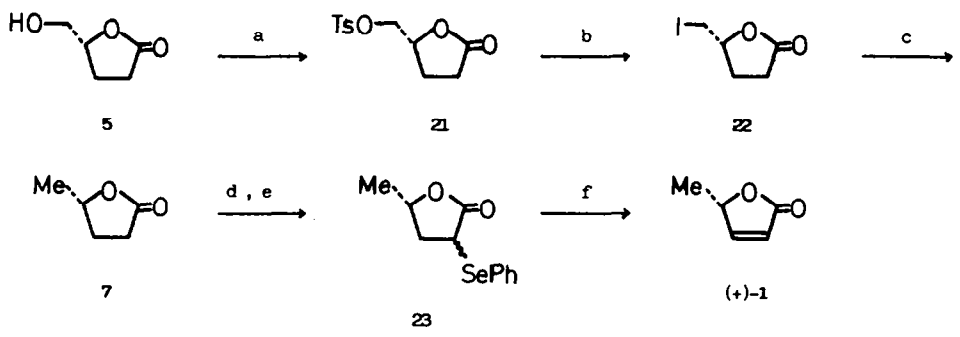


Reagents.- a: MeOH, H_2SO_4, CH_2Cl_2; b: $Me_2C(OMe)_2$, acetone, p-TsOH; c: KOH, MeOH; d: BH_3-THF, 0°; e: TsCl, pyr; f: $LiAlH_4$, ether; g: MeOH, Lewatit S-100 resin; h: NaCN, DMSO; i: HCl sat MeOH; j: MsCl, Et_3N, CH_2Cl_2, 0°.

Scheme 2

From the retrosynthetic analysis shown in Scheme 1, an alternative route to (+)-1 starts from hydroxymethylbutanolide **5**, that is, in turn, the precursor of (S)-γ-valerolactone, **7**. Creation of the C-C double bond in this case could imply elimination of phenylselenenic acid from a α-phenylselenoderivative.

Hydroxylactone **5** can be synthetized from several chiral materials. The more direct way starts from unnatural (R)-glutamic acid, **17**, and implies cyclization to a lactonic acid, followed by chemoselective reduction of the free carboxyl group.[15] Also, since conversion of (S)-γ-hydroxymethyl-γ-butyrolactone, **18**, into its enantiomer, **5**, has been reported,[16] preparation of **5** from cheaper natural (S)-glutamic acid,[17] **19**, can be accomplished. Moreover, **18** has been obtained by hydrogenation of (S)-γ-hydroxymethylbutenolide, **20**, synthetized in turn from D-ribonolactone, **3**.[18] Thus, this sugar derivative can serve as chiral precursor of both enantiomeric β-angelica lactones, (+)- and (-)-**1**.



Reagents.- a: TsCl, pyr; b: NaI, acetone; c: H_2, Pd/C, EtAcO; d: LDA, -78°; e: PhSeBr, -78°; f: 30% aq H_2O_2, HAcO, THF.

Scheme 3

Transformation of 5 into 7 had been previously effected by Mori in a synthesis of sulcatol[19] (Scheme 3), based in tosylation of 5, substitution of the tosiloxy group by iodide and hydrogenolysis with Raney nickel. We have followed this method but performing the last reaction with hydrogen and Pd/C as catalyst, resulting in an improved yield of (S)-γ-valerolactone, 7. Reaction of 7 with LDA and phenylselenyl bromide gave the new compound 23 as a liquid diastereoisomeric mixture, that by oxidation and subsequent pyrolysis led to (+)-1 in 25 % overall yield from 5 (13 % and 15 % overall yield from (S)-glutamic acid and D-ribonolactone, respectively).

Thus, we have reported hereupon two convenient methods for the preparation of (S)-β-angelica lactone that have moderate overall yields and use easily available raw materials as L-tartaric acid, (S)-glutamic acid or D-ribonolactone.

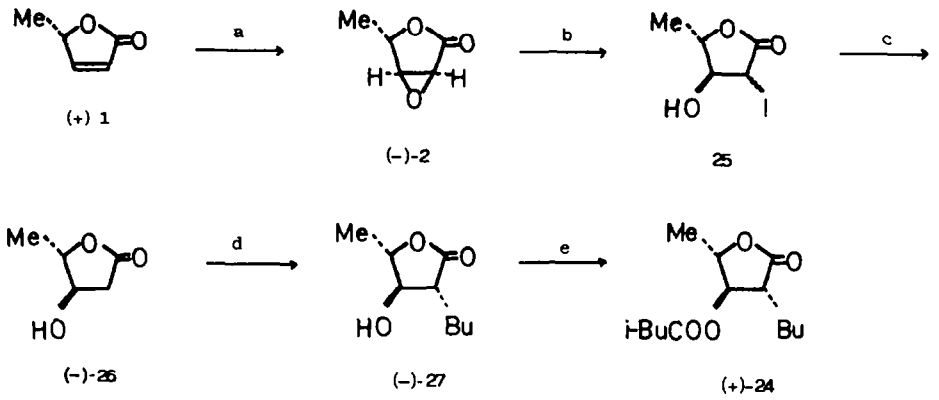
2. Enantiomeric β-angelica epoxides, (+)-2 and (-)-2

α,β-Butenolides are inert to epoxidation by peracids, and the presence of the lactone function precludes the use of hydrogen peroxide as epoxidation agent since it requires basic conditions. The method utilized by Tishler *et al.*[20] has proved in our hands to be effective only with γ-alkyl-α,β-butenolides. Thus, (R)-β-angelica lactone, (-)-1 was treated with sodium hypochlorite in pyridine affording stereoselectively the epoxy derivative (+)-2 as a liquid, b.p. 115°/18 torr, $[\alpha]^{22}_D$ = +42.1 (c = 3.28, CH_2Cl_2), along with some α,β-epoxy-γ-hydroxyacid, that results from lactone ring opening under the reaction conditions. This acid is readily cyclized into (+)-2 being then the overall yield of the epoxidation 54 %.[21] In the same way, (S)-β-angelica lactone, (+)-1, underwent epoxidation affording (-)-2, $[\alpha]^{20}_D$ = -40.12 (c = 3.34, CH_2Cl_2). (Scheme 4).

However, when γ-hydroxymethyl-α,β-butenolide, 20, or its methyl ether derivative were subjected to the same epoxidation conditions, no defined products were found.[22]

3. (+)- and (-)-Blastmycinone, 24

Blastmycinone, 24, seemed an easily available synthetic target using β-angelica lactone epoxide, 2, as precursor. Indeed, blastmycinolactol, 27, could come from regio- and stereocontrolled oxirane ring opening by the action of a suitable nucleophile. In our laboratory, we have explored the behaviour of 2 toward several nucleophiles,[23] and we have verified that the reaction with lithium dibutylcuprate afforded blastmycinolactol, 27, in only 15 % yield.[21,23] For this reason, we decided to investigate a second synthetic pathway, that, although longer, could result in a better overall yield. The sequence is depicted in Scheme 4 and passes through hydroxylactone 26, as a key intermediate. The direct conversion of the epoxylactone 2 into 26 could not be performed. Thus, attempts to reductive oxirane ring opening under medium pressure catalytic hydrogenation conditions -even in the presence of a protic acid- let unaltered the product. Reaction with sodium borohydride gave prior reduction of the carbonyl group.[23] However, 26



Reagents.- a: NaOCl, pyr; b: NaI, NaAcO, HAcO, acetone; c: H_2, Pd/C, EtAcO; d: BuI, HMPA, THF, -40°; e: i-BuCOCl, pyr.

Scheme 4

was obtained in very good yield by two steps transformation of 2: ring opening by iodide anion giving the diastereoisomeric mixture of iodides 25 and quantitative hydrogenolysis of this mixture. The lithium enolate of (+)-26,[8] prepared from (+)-2, was stereoselectively alkylated to afford (+)-blastmycinolactol,[24b] (+)-27, $[\alpha]_D^{22}$ = +19.5 (c = 1.95, $CHCl_3$), that gave, by esterification with isovaleryl chloride, (-)-blastmycinone[24b] (-)-24, $[\alpha]_D^{22}$ = -9.4 (c = 1.70, $CHCl_3$), in 50 % overall yield from the epoxy derivative 2.

This sequence has been performed independently on the two epoxylactone enantiomers, giving rise to both (+)- and (-)-blastmycinones.

(+)-Blastmycinone[24] is a metabolite derived from the antibiotic Antymicine A complex, effective against fungi and yeasts.[4]

Studies on the preparation of other interesting trisubstituted γ-methyl-γ-butyrolactones, using the β-angelica lactones epoxides described herein, are in progress.

EXPERIMENTAL SECTION

Melting points have been determined on a Kofler hot stage and are uncorrected. Optical rotations were obtained on a Propol polarimeter, model Dr. Kernchen. Distillation of small amounts were effected on a rotational distillator Büchi, model KRV 65/30 (only external or oven temperature given). The 70 ev electron impact mass spectra were recorded with a Hewlett-Packard apparatus, model 5985 B. The infrared spectra were recorded on a Perkin-Elmer spectrophotometer, model 1310. The 80 MHz ^1H and 20 MHz ^{13}C NMR spectra were recorded on a Bruker Spectrometer, model WP 80 SY; chemical shifts are given in parts per million relative to TMS (δ scale).

(-)-[Methyl 4-O-p-toluenesulfonyl-2,3-O-isopropylidene-L-threonate], 12.[25] To a solution of 11 (1.7 g, 8.9 mmol) in dry pyridine (25 ml) tosyl chloride (3.4 g, 17.7 mmol) was added and the mixture was stirred for 2.5 h at 0° and for 3 h at r.t. Then the reaction mixture was poured into 157 ml of 2.5 M aq HCl and the resulting solution was extracted with four 250 ml portions of CH_2Cl_2. The combined organic layers were washed with 1 M aq HCl (100 ml) and sat aq sodium bicarbonate (100 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel, using CH_2Cl_2 as eluent, to afford 2 g (66 % yield) of the tosylate 12, m.p. 47-49° (from hexane), $[\alpha]_D^{20}$ = -22.12° (c = 0.68, methanol) and -18.80° (c = 0.54, chloroform); ^1H NMR ($CDCl_3$) 1.37 (s, 6H), 2.37 (s, 3H), 3.65 (s, 3H), 4.21 (complex absorption, 4H), 7.12 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H); ^{13}C NMR 21.4, 25.7, 26.6, 52.3, 68.4, 75.2, 76.4, 112.1, 127.9, 129.7, 132.9, 144.9, 170.1; IR (film) 3005, 2970, 1760, 1600, 1440, 1370, 935 cm^{-1}; MS, m/e 329 (100), 227 (19), 155 (55), 113 (11), 91 (72), 65 (19), 59 (15), 43 (39).

4-Deoxy-2,3-O-isopropylidene-L-threytol, 13.[25]
To an ice-cooled solution of 12 (1.3 g, 3.8 mmol) in anhydrous ether (10 ml) a suspension of $LiAlH_4$ (0.8 g, 21 mmol) in 28 ml of ether was added over a 30 min period and the mixture was stirred overnight at r.t. Then 1 ml of water, 1 ml of 20 % aq NaOH, 14 ml of THF and 3 ml of water were successively added to the ice-cooled reaction mixture. After stirring for 1 h at r.t. the precipitated salts were filtered and washed with 300 ml of ether. The solvents were evaporated at reduced pressure and the residue was chromatographed on silica gel (methylene chloride-methanol (95:5) as eluent) to afford 13 as an oil that was unsuitable for optical rotation measurements (0.5g, 85 % yield). ^{1}H NMR ($CDCl_3$) 1.27 (d, J = 6 Hz, 3H), 1.43 (complex absorption, 6H), 1.89 (broad signal, 1H), 3.46-4.20 (m, 4H); ^{13}C NMR ($CDCl_3$ 17.6, 26.8, 27.2, 61.6, 73.0, 82.9, 108.4; IR (film) 3700-3070 (broad), 3005, 2960, 2890, 1460, 1380, 1240, 1180, 1100, 1000, 885 cm^{-1}; MS, m/e 131 (27), 115 (7), 71 (21), 45 (44), 44 (39), 43 (100).

(-)-1-O-p-Toluenesulfonyl-4-deoxy-2,3-O-isopropylidene-L-threytol, 14.[25]
Following the procedure described above for the preparation of compound 12, the tosylate 14 was obtained in 85 % yield, as a solid, m.p. 79.5-80.5° (from hexane), $[\alpha]_D^{20}$ = -2.30° (c = 2.47, chloroform); ^{1}H NMR ($CDCl_3$) 1.25 (d, J = 8 Hz, 3H), 1.26 (s, 6H), 2.36 (s, 3H), 3.93 (d, J = 4 Hz, 2H), 3.94-3.31 (m, 2H); 7.02 (d, J = 7.5 Hz, 2H); 7.45 (d, J =7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) 17.8, 21.5, 26.6, 27.2, 68.7, 74.1, 79.4, 109.2, 127.9, 129.8, 133.1, 144.9; IR (film) 3000, 2950, 1600, 1450, 1360, 1240, 1180, 1100, 990 cm^{-1}; MS, m/e 285 (12), 217 (7), 216 (11), 173 (100), 155 (65), 92 (39), 91 (94), 75 (30), 65 (32), 45 (18), 43 (24).

(-)-1-O-p-Toluenesulfonyl-4-deoxy-L-threytol, 15.
A solution of 14 (0.5 g, 1.7 mmol) in 35 ml of anhydrous methanol, in the presence of Lewattit S-100 sulfonic resin, was heated to reflux for 15 h. The resin was filtered out and the solvent was removed at reduced pressure. The residue was chromatographed on silica gel (3:1 methylene chloride-ethyl acetate as eluent) to afford 15 (0.4 g, 85 % yield), m.p. 82-83° (from pentane); $[\alpha]_D^{20}$ = -1.97° (c = 0.40, chloroform); ^{1}H NMR ($CDCl_3$) 1.2 (d, J = 7.4 Hz, 3H), 2.26 (Broad signal, 2H), 2.46 (s, 3H), 3.75 (m, 2H), 4.09 (dd, J = 5.0 Hz, J' = 1.4 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.8 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) 19.1, 21.4, 67.0, 71.2, 73.0, 127.8, 129.9, 132.6, 145.0; IR (KBr) 3600-3100 (broad), 2970, 2920, 1590, 1440, 1395, 1345, 1175, 1150, 1080, 1055, 1005, 965, 870 cm^{-1}; MS, m/e 261 (M+1, 0.7), 216 (11), 173 (100), 155 (53), 91 (93), 92 (43), 75 (21), 65 (41), 57 (11), 45 (60). Anal. Calc. for $C_{11}H_{16}O_5S$:C, 50.76; H, 6.19; S, 12.32. Found: C, 50.98; H, 6.20; S, 12.53.

(-)-(4S,5S)-4-Hydroxy-5-methyldihydro-2(3H)-furanone, 6, through nitrile 16.
To a solution of tosylate 15 (0.2 g, 0.9 mmol) in 5 ml of DMSO (freshly distilled over calcium hydride) sodium cyanide (0.1 g, 1.9 mmol) was added and the mixture was stirred for 72 h at r.t. Most DMSO was evaporated at 40.5°/1 torr and the residue was washed with chloroform (40 ml). Elimination of the solvent at reduced pressure gave a residue that , after chromatography on silica gel (9:1 methylene chloride-ethyl acetate as eluent) and subsequent distillation (96°/0.1 torr) gave the nitrile 16 (65 mg, 64 % yield) as a viscous oil, $[\alpha]_D^{20}$ = -0.66° (c = 2.10, chloroform); ^{1}H NMR ($CDCl_3$) 1.21 (d, J = 6.6 Hz, 3H); 2.58 (d, J = 6.0 Hz, 2H); 3.44-3.88 (complex absorption, 2H), 4.14 (s, 2H); ^{13}C NMR ($CDCl_3$) 19.2, 22.6, 69.2, 75.3, 117.7; IR (film) 3680-3020 (broad), 2250, 1410, 1135, 1065, 995, 900 cm^{-1}; MS, m/e 116 (M, 1), 98 (2), 88 (8), 75 (23), 71 (43), 57 (38), 45 (79), 44 (100), 43 (30), 42 (33).

A solution of nitrile 16 (47 mg, 0.4 mmol) in 4 ml of HCl sat methanol was heated to reflux for 2 h. The solution was concentrated at reduced pressure to one half of its volume and 2 ml of water were added. After stirring overnight at r.t. 10 ml of water were added and the solution was refluxed for 30 min and extracted with three 25 ml portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and the solvents were removed under vacuum. The residue was chromatographed on silica gel (1:1 hexane-ethyl acetate as eluent) to afford 19 (30 mg, 64 % yield) as an oil, $[\alpha]_D^{20}$ = -73.7° (c = 1.60, ethanol).(Lit[26] $[\alpha]_D$ = +75° (c = 0.25, ethanol) for the enantiomer); ^{1}H NMR ($CDCl_3$) 1.43 (d, J = 7.5 Hz, 3H), 2.51 (dd, J = 17.5 Hz, J' = 1.2 Hz, 1H), 2.84 (dd, J = 17.5 Hz, J' = 4.4 Hz, 1H); 2.91 (s, 1H); 4.35-4.72 (complex absorption, 2H); IR (film) 3680-3030 (broad), 2980, 2930, 1770, 1340, 1170, 1135, 1100, 1055, 990, 940 cm^{-1}; MS, m/e 117 (M+1, 1), 88 (39), 71 (5), 57 (13), 45 (49), 44 (100), 43 (56).

(-)-(S)-5-Methyldihydro-2(3H)-furanone, 7.
Iodolactone 22[19] (3g, 13.1 mmol) in 90 ml of ethyl acetate was hydrogenated at 2.5 atmospheres in the presence of potassium bicarbonate (1.1 g, 13.1 mmol) and 10 % palladium on charcoal (300 mg). After five days the mixture was filtered, the solid phase washed with 300 ml of ethyl acetate and the organic layers were washed with sat aq NaCl and dried over sodium sulfate. Evaporation of the solvent at reduced pressure gave crude 7 that was distilled at 100°/15 torr to afford pure 7 (0.9 g, 66 % yield); $[\alpha]_D^{20}$ = -32.7° (c = 1.85, methylene chloride).(Lit[19] $[\alpha]_D^{20}$ = -29.6 (c = 1.29, methylene chloride). Spectral data (IR, ^{1}H NMR) for this material are consistent with those previously published[19].

(3RS,5S)-3-Phenylseleno-5-methyldihydro-2(3H)-furanone, 23.
To a stirred solution of diisopropylamine (0.77 ml, 5.5 mmol) in anhydrous THF (7 ml) cooled at 0° under argon, 3.4 ml (5.5 mmol) of a 1.6 M solution of butyllithium in hexane were added. After 30 min the mixture was cooled to -78° and lactone 7 (240 mg, 2.4 mmol) in 8 ml of THF was added. After stirring for 35 min phenylselenyl bromide (2.6 mmol, prepared from 412 mg of diphenyldiselenide and 211 mg of bromine) in 5 ml of THF was added. After 1.5 h, sat aq ammonium chloride (6 ml) and sat aq NaCl (6 ml) were added at -78° and the mixture was allowed to reach r.t. and then extracted with three 50 ml portions of ethyl acetate. The combined organic layers were successively washed with 15 ml of 10 % aq HCl, 15 ml of water, 20 ml of sat aq NaCl, 20 ml of 10 % aq sodium bisulfite, 15 ml of water and finally with 15 ml of sat aq NaCl. After drying over sodium sulfate the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (methylene chloride as eluent), to give 380 mg (62 % yield) of the diastereoisomeric mixture 23, as a syrup.

^{1}H NMR ($CDCl_3$) 1.30 (d, J = 5.9 Hz) and 1.39 (d, J = 5.9 Hz)(3H); 1.63-2.96 (complex absorption, 2H); 3.98 (m, 1H); 4.47 (m, 1H); 7.31 (m, 3H); 7.65 (m, 2H); IR (film): 2970, 2930, 1755, 1570, 1470, 1435, 1380, 1335, 1290, 1180, 1115, 1075, 1045, 1020, 1000, 940 cm^{-1}; MS, m/e 258 (14), 256 (63), 254 (37), 253 (14), 252 (13), 158 (36), 157 (18), 156 (19), 155 (18), 154 (11), 131 (17), 99 (22), 77 (20), 55 (100). Anal. Calc. for $C_{11}H_{12}O_2Se$: C, 51.78; H, 4.74. Found: C, 51.78, H, 4.75.

(+)-(5)-β-angelica lactone, (+)-1.

a) From hydroxylactone 6. To an ice-cooled solution of hydroxylactone 6 (26 mg, 0.2 mmol) and triethylamine (0.08 ml, 0.6 mmol) in methylene chloride (1.5 ml) mesyl chloride (0.03 ml, 0.4 mmol) was added. After stirring for 1 h at 0° the mixture was diluted with methylene chloride (10 ml) and washed with water (5 ml), then with two 2 ml portions of 2.5 M aq HCl and finally with two 5 ml portions of sat aq NaCl, and then dried over sodium sulfate. The solvent was removed at reduced pressure and the crude was chromatographed on silica gel (3:2 hexane-methylene chloride as eluent) to afford (+)-1 (20 mg, 94 % yield) as a liquid, b.p. 98-100°/15 torr, $\{\alpha\}_D^{20}$ = +93.83° (c = 0.5, chloroform)(lit[4] $\{\alpha\}_D^{26}$ = -95.9° (c =0.7, chloroform) for the enantiomer); ^{1}H NMR ($CDCl_3$) 1.44(d, J = 6.9 Hz, 3H), 5.12 (m, 1H), 6.07 (dd, J = 5.5 Hz, J' = 1.8 Hz, 1H), 7.41 (dd, J = 5.5 Hz, J' = 1.9 Hz, 1H); IR (film): 3100, 2990, 2940, 1770, 1600, 1450, 1320, 1165, 1105, 1075, 1030, 960 cm^{-1}; MS, m/e 98 (95), 85 (12), 83 (82), 69 (9), 55 (100), 54 (26), 43 (62).

b) From selenyde 23. To an ice-cooled solution of diastereoisomeric mixture 23 (377 mg, 1.5 mmol) in 9 ml of THF some drops of acetic acid and 30 % aq hydrogen peroxide (1 ml, 8.9 mmol) were successively added and the mixture stirred for 30 min. Then, the solution was neutralized to pH slightly basic with sat aq sodium bicarbonate. The aqueous layer was extracted with three 40 ml portions of ether and the combined organic layers were dried over sodium sulfate and the solvents removed at reduced pressure. The residue was distilled at 96-100°/14 torr, affording quantitatively 145 mg of (+)-1.

(-)-(3S,4S,5S)-3,4-Epoxy-5-methyldihydro-2(3H)-furanone, (-)-2.

To an ice-cooled solution of (+)-1 (246 mg, 2.5 mmol) in pyridine (11 ml) aqueous sodium hypochlorite (8.84 ml of a solution containing 50.3 g/l of chlorine, 6.28 mmoles) was added. The reaction mixture was stirred at 0° for 1 h and for 1.5 h at r.t. Then, aq sodium bicarbonate (4 ml of a 1 M solution) was added and the resulting solution extracted with methylene chloride (35 ml). The organic layer was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to give 80 mg of (-)-2. The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid, saturated with ammonium sulfate and extracted with six 30 ml portions of ethyl acetate. The organic phase was dried and the solvent evaporated to afford a mixture of (2S,3S,4S)-2,3-epoxy-4-hydroxypentanoic acid, and epoxylactone (-)-2 (220 mg). The combined crudes were distilled at 95-105°/0.2 torr giving 187 mg of (-)-2 contaminated with some impurity. Chromatography on silica gel (3:7 methylene chloride-hexane as eluent) afforded pure (-)-2 (168 mg, 59 % yield) as a liquid, b.p. 115°/18 torr, $\{\alpha\}_D^{20}$ = -40.12° (c = 3.3, methylene chloride); ^{1}H NMR ($CDCl_3$) 1.42 (d, J =6.7 Hz, 3H); 3.79 (dd, J =2.5 Hz, J' = 0.7 Hz, 1H); 3.96 (d, J =2.5 Hz, 1H); 4.69 (dq, J = 6.7 Hz, J' = 0.7 Hz, 1); ^{13}C NMR ($CDCl_3$) 17.2, 49.5, 58.5, 76.0, 170.0; IR (film) 3060, 2970, 1770, 1450, 1335, 1280, 1180, 1065, 985, 940 cm^{-1}; MS, m/e 114 (26), 99 (4), 71 (9), 69 (100), 43 (47), 42 (57), 41 (70), 39 (41). Anal. Calc. for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.39; H, 5.19.

(+)-(3R,4R,5R)-3,4-Epoxy-5-methyldihydro-2(3H)-furanone, (+)-2.

Compound (+)-2 was prepared as described above for the enantiomer. $\{\alpha\}_D^{20}$ = +42.07° (c = 3.3, methylene chloride).

Diastereoisomeric mixture of (3R,4S,5S)- and (3S,4S,5S)-3-iodo-4-hydroxy-5-methyldihydro-2(3H)-furanone, 25.

To an ice-cooled solution of epoxide (-)-2 (83.6 mg, 0.73 mmoles) in acetone (7 ml), sodium iodide (1.1 g, 7.3 mmoles), sodium acetate (3.0 mg, 3.7 mmol) and acetic acid (0.2 ml, 3.7 mmol) were successively added. The mixture was stirred for 30 min at 0° and for 2 h at r.t. Then ethyl acetate (20 ml) and 10 % aq solution of sodium thiosulfate (4 ml) were added, the resulting mixture shaken and the layers separated. The organic layer was washed with two 15 ml portions of saturated aq sodium bicarbonate and with 10 ml of sat aq sodium chloride and dried over sodium sulfate. The solvent was removed to give a crude containing the diastereoisomeric mixture 25 (161 mg) that was chromatographed through silica gel (mixtures of hexane-ethyl acetate as eluents) giving pure 25 (128 mg, 72 % yield). ^{1}H NMR ($CDCl_3$) 1.53 (d, J = 6.3 Hz) and 1.58 (d, J = 6.3 Hz)(3H); 2.63-2.85 (broad signal, 1H); 3.26 (m) and 4.05-4.83 (complex absorption)(3H); IR (film) 3700-3025 (broad), 2980, 2925, 1760, 1445, 1380, 1180, 1130, 1055, 1000, 950 cm^{-1}. By the same procedure, the mixture of (3R,4R,5R)- and (3S,4R,5R)-iododerivatives was prepared.

(-)-(4R,5S)-4-Hydroxy-5-methyldihydro-2(3H)-furanone, (-)-26.

The mixture of iodides 25 (126 mg, 0.52 mmol) in 15 ml of ethyl acetate was hydrogenated at 2.6 atmospheres in the presence of potassiun carbonate (144 mg, 1.04 mmol) and 10 % palladium on charcoal (22 mg). After 72 h the mixture was filtered and the solvent removed affording 66 mg of a residue that was filtered through silica gel to give (-)-26 (46 mg, 76 % yield) as a liquid, b.p. 125°/12 torr, $\{\alpha\}_D^{20}$ = -10.81 (c = 1.85, chloroform); ^{1}H NMR[27] ($CDCl_3$) 1.37 (d, J = 6.3 Hz, 3H); 1.46-1.76 (broad signal, 1H); 2.47 (dd, J =17.8 Hz, J' = 3.9 Hz, 1H); 2.87 (dd, J = 17.8 Hz, J' = 6.2 Hz, 1H); 4.25 (m, 1H); 4.50 (dq, J = 6.3 Hz, , J' = 2.8 Hz, 1H); IR (film) 3700-3015 (broad), 2970, 2925, 1750, 1445, 1355, 1180, 1100, 1050, 995, 935 cm^{-1}. Hydroxylactone (+)-26 was prepared in a simmilar manner as described above for its enantiomer. $\{\alpha\}_D^{22}$ = + 10.2 (c = 2.60, chloroform).(Lit[8] $\{\alpha\}_D^{20}$ = +10.87 (c = 2.42, chloroform).

(+)-Blastmycinolactol, (+)-27.

To a stirred and ice-cooled solution of diisopropylamine (1.46 ml, 10.4 mmol) in anhydrous THF (15 ml) under argon, 7.2 ml (11.51 mmol) of a 1.6 M solution of butyllithium in hexane was added dropwise. After 30 min the mixture was cooled to -78° and a solution of (+)-26 (550 mg, 4.74 mmol)

in THF (4.5 ml) was added dropwise over a 14 min period. The mixture was stirred at -78° for 45 min and then butyl iodide (1.2 g, 6.64 mmol) in 4 ml of hexamethylphosphorotriamide and 4 ml of THF was added. After stirring for 20 min at -78° and 5 h at -40° the mixture was hydrolyzed with 11 ml of 1 M HCl, allowed to reach r.t. while stirring and diluted with 80 ml of ethyl acetate. The layers were separated and the organic layer was washed twice with 15 ml portions of sat aq NaCl and dried over sodium sulfate. The solvents were removed under reduced pressure and the residue was chromatographed through silica gel (mixtures of hexane-ethyl acetate as eluents) to afford 230 mg of unaltered (+)-26 and 286 mg of (+)-27 (60 % yield based on the transformed starting material, m.p. 54-55° (from ether-pentane), $[\alpha]_D^{22}$ = + 19.5° (c = 1.95, chloroform).(Lit[24b] m.p. 50-51°, $[\alpha]_D^{23}$ = + 16° (c = 1.09, methanol); ^{1}H NMR ($CDCl_3$) 0.90 (m, 3H); 1.13-1.97 (complex absorption, 6H), 1.42 (d, J = 6.2 Hz, 3H); 2.57 (m, 1H); 2.66 (s, 1H); 3.81 (dd, J = 8.5 Hz, J' = 7.0 Hz, 1H); 4.17 (dq, J = 7.0 Hz, J' = 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.7, 18.2, 22.5, 28.1, 28.7, 48.7, 78.7, 80.7, 177.3; IR ($CHCl_3$) 3625, 3590-3250 (broad), 2970, 2940, 2880, 1780, 1460, 1390, 1175, 1055 cm^{-1}; MS, m/e 173 (M+1, 4), 155 (2), 129 (12), 116 (99), 100 (42), 99 (76), 82 (43), 71 (39), 57 (100), 43 (49).

(-)-Blastmycinone, (-)-24.
To a stirred and ice-cooled solution of (+)-27 (118 mg, 0.69 mmol) in anhydrous pyridine (7 ml) isovaleryl chloride (0.25 ml, 2.06 mmol) was added. After stirring for 24 h at r.t. the mixture was poured dropwise into ice-water (20 ml) with vigorous stirring and the resulting solution was extracted with ethyl acetate (100 ml). The layers were separated and the organic layer was washed with 2 M HCl, then with 15 ml of 10 % aq sodium bicarbonate and finally with sat NaCl (20 ml), and then dried over sodium sulfate. The solvent was removed at reduced pressure and the crude was chromatographed on silica gel (5:95 ethyl acetate-hexane as eluent) to afford (-)-24 (150 mg, 85 % yield) as a colorless oil, b.p. 95-97°/0.2 torr, $[\alpha]_D^{22}$ = -9.41° (c = 1.70, chloroform).(Lit[24b] $[\alpha]_D^{25}$ = -10° (c = 1.20, chloroform); ^{1}H NMR ($CDCl_3$) 0.75-1.09 (complex absorption, 9H); 1.17-2.33 (complex absorption, 9H); 1.47 (d, J = 6.5 Hz, 3H); 2.68 (m, 1H); 4.37 (dq, J = 6.5 Hz, J' = 4.6 Hz, 1H); 4.95 (dd, J = 5.7 Hz, J' = 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.5, 19.2, 22.1, 22.2, 25.5, 28.7, 28.8, 43.0, 46.3, 78.4, 79.0, 172.1, 175.4; IR ($CHCl_3$) 2960, 2940, 2880, 1775, 1735, 1460, 1290, 1175, 1115, 1040, 960 cm^{-1}; MS, m/e 257 (M+1, 76), 200 (23), 155 (36), 99 (52), 85 (100), 57 (59), 43 (62), 41 (73).

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NOTES AND REFERENCES

1. S. Hanessian, "Total synthesis of natural products. The chiron approach". Pergamon Press, 1983.
2. J. Cardellach, J. Font and R. M. Ortuño, J. Heterocycl. Chem., 21, 327 (1984).
3. J. C. V. Martínez, M. Yoshida, O. R. Gottlieb, Tetrahedron Lett., 1979, 1021.
4. M. Kinoshita, S. Aburaki and S. Umezawa, J. Antibiotics, 25, 373 (1972) and references therein.
5. K. Takeda, K. Sakuravi and H. Ishii, Tetrahedron, 28, 3757 (1972).
6. B. N. Ravi and J. Wells, Aust. J. Chem., 35, 107 (1982).
7. P. Camps, J. Cardellach, J. Corbera, J. Font, R. M. Ortuño and O. Ponsatí, Tetrahedron, 39, 395 (1983).
8. S. Chen and M. M. Joullié, J. Org. Chem., 49, 2168 (1984).
9. Previous communication: R. M. Ortuño, D. Alonso and J. Font, Tetrahedron Lett., 27, 1079 (1986).
10. J. A. Musich and H. Rapopport, J. Amer. Chem. Soc., 100, 4865 (1978).
11. a) G. Zweifel and H. C. Brown, Organic Reactions, 13, 1 (1963); b) H. C. Brown and R. L. Sharp, J. Amer. Chem. Soc., 90, 2915 (1968).
12. A. Tanada and K. Yamashita, Chemistry Lett., 1982, 319.
13. J. Font, R. M. Ortuño, O. Ponsatí and F. Sánchez-Ferrando, Nouv. J. Chim., 6, 305 (1982).
14. S. Takano, M. Morimoto and K. Ogasawara, Synthesis, 1984, 834.
15. C. Eguchi, A. Kakuta, Bull. Chem. Soc. Jpn., 47, 1704 (1974).
16. P. T. Ho and N. Davies, Synthesis, 1983, 462.
17. M. Taniguchi, K. Koga and S. Yamada, Tetrahedron, 30, 3547 (1974).
18. P. Camps, J. Cardellach, J. Font, R. M. Ortuño and O. Ponsatí, Tetrahedron, 38, 2395 (1982).
19. K. Mori, Tetrahedron, 31, 3011 (1975).
20. A. A. Jakubowski, F. S. Guziec, M. Sugiura, C. C. Tam and M. Tishler, J. Org. Chem., 47, 1221 (1982).
21. Previous communication: J. Cardellach, J. Font and R. M. Ortuño, Tetrahedron Lett., 26, 2815 (1985).
22. R. Mercé, Ph. D. Thesis, Universitat Autònoma de Barcelona.
23. R. M. Ortuño, J. Cardellach and J. Font, J. Heterocycl. Chem., in press.
24. Previous synthesis of optically active blastmycinone: a) M. Kinoshita, S. Aburaki, M. Wada and S. Umezawa, Bull. Chem. Soc. Jpn., 46, 1279 (1973);b) S. Aburaki, N. Konishi and M. Kinoshita, Bull. Chem. Soc. Jpn.,48, 1254 (1975); c) T. Fujisawa, H. Kohama, K. Tajima and T. Sato, Tetrahedron Lett., 1984, 5155.
25. Suntory Ltd. Jpn. Kokai Tokkyo Koho JP 57,158,777 (82, 158, 778). Chem Abstracts, 98, 160692d (1983).
26. R.E. Moore, A. J. Blackman, C. E. Chenk and J. S. Mynderse, J. Org. Chem., 49, 2484 (1984).
27. C. Gennari, A. Bernardi, S. Cardami and. C. Scolastico, Tetrahedron, 40, 4059 (1984). Only the ^{1}H NMR spectrum is described.