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SYNTHESIS OF (±)-RAMULOSIN VIA INVERSE TYPE HETERO-DIELS-ALDER REACTION [1]

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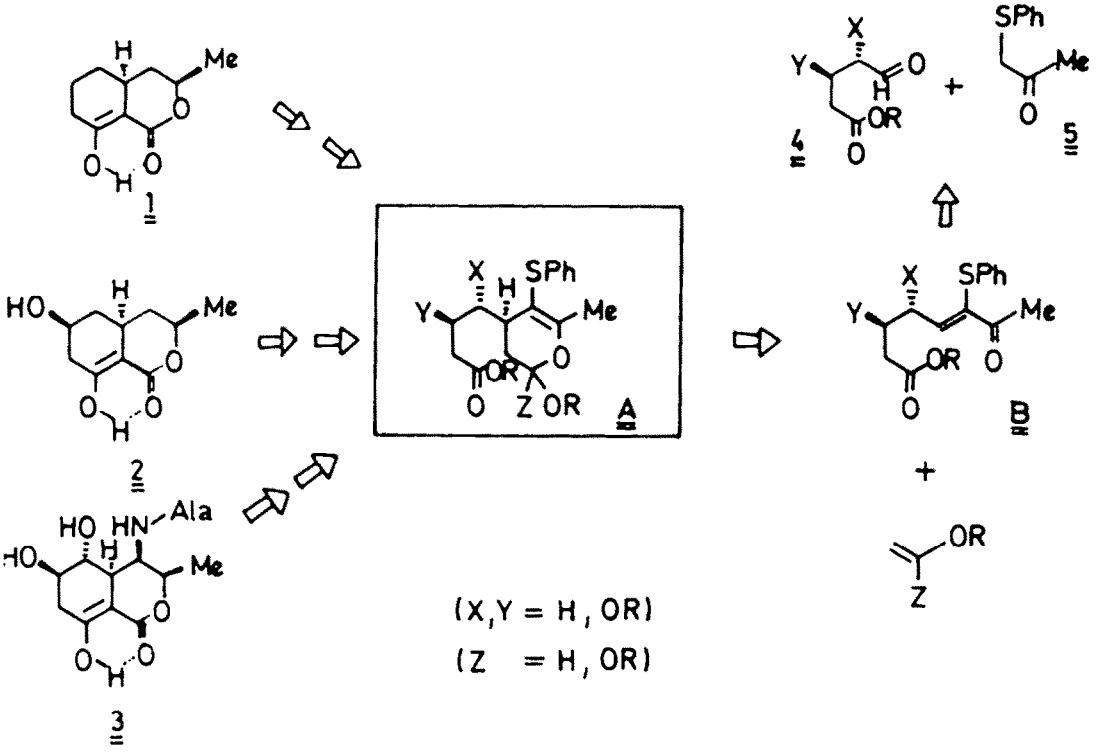
Abstract - Condensation of 4-formylbutanoates (4a,b) with phenylthioacetone (5) provided the 1-oxa-1,3-diene derivatives 6a,b which afforded in high yielding inverse type hetero-Diels-Alder reactions with vinyl ethers and ketene acetals the desired dihydropyran cycloadducts 7a-c and 11a-c, respectively. The target molecule (±)-ramulosin 1 was obtained from compounds 11a and 7a inconvenient chemo- and diastereoselective three and four step transformations.

The efficiency and versatility of inverse type hetero-Diels-Alder reactions of δ-acyloxy-α-phenylthio substituted α,β-unsaturated carbonyl compounds as 1-oxa-1,3-dienes with enol ethers and derivatives as heterodienophiles have been demonstrated in various de novo-syntheses of important natural carbohydrates including rare deoxy sugars, C-aryl glycopyranosides, and 3-deoxy-2-glyculosonates. [2-7] In this strategy diastereospecific generation of up to five chiral centers in three steps with preferential formation of one enantiomer was possible. [2-4,6]

The general usefulness of this methodology can be verified in different areas. Thus, chemoselective reactions could be also carried out with δ-unsubstituted α-phenylthio substituted α,β-unsaturated carbonyl compounds and enol ethers leading to natural 2,3,6-trideoxy and to 4-amino-2,3,4,6-tetradeoxy sugars quite readily. [8] The efficiency of this approach with carbon substituents at the δ-position will be exampled in this paper for the synthesis of the antibiotic ramulosin (1, Scheme 1). [9] This approach should be also applicable to the synthesis of the biogenetically related antibiotics hydroxyramulosin (2) and actinobolin (3) [10] which gained recently importance because of interesting biological properties. Ramulosin (1) and hydroxyramulosin (2) have first been isolated from the fungus Pestalotra ramulosa [11,12]; ramulosin was later also found in other species. [13] It inhibits the germination of seeds and spores of microorganisms. [14] The first synthetic approach led to the diastereoisomer epiramulosin [15] (see compound 15 in Scheme 2). A seven step synthesis of the racemate was developed by Cordova and Snider. [16] Actinobolin (3) was isolated from Streptomyces griseoviridis [17] and its structure determined by different groups. [18] It has broad spectrum antibiotic and moderate antitumor activity. It is a potential cariostatic agent. [19] It is

* This paper is dedicated to Professor E.C. Taylor on the occasion of his 65 th birthday.

structurally related to the very promising antitumor agent bactobolin [20] therefore several syntheses of this compound have been reported. [21]



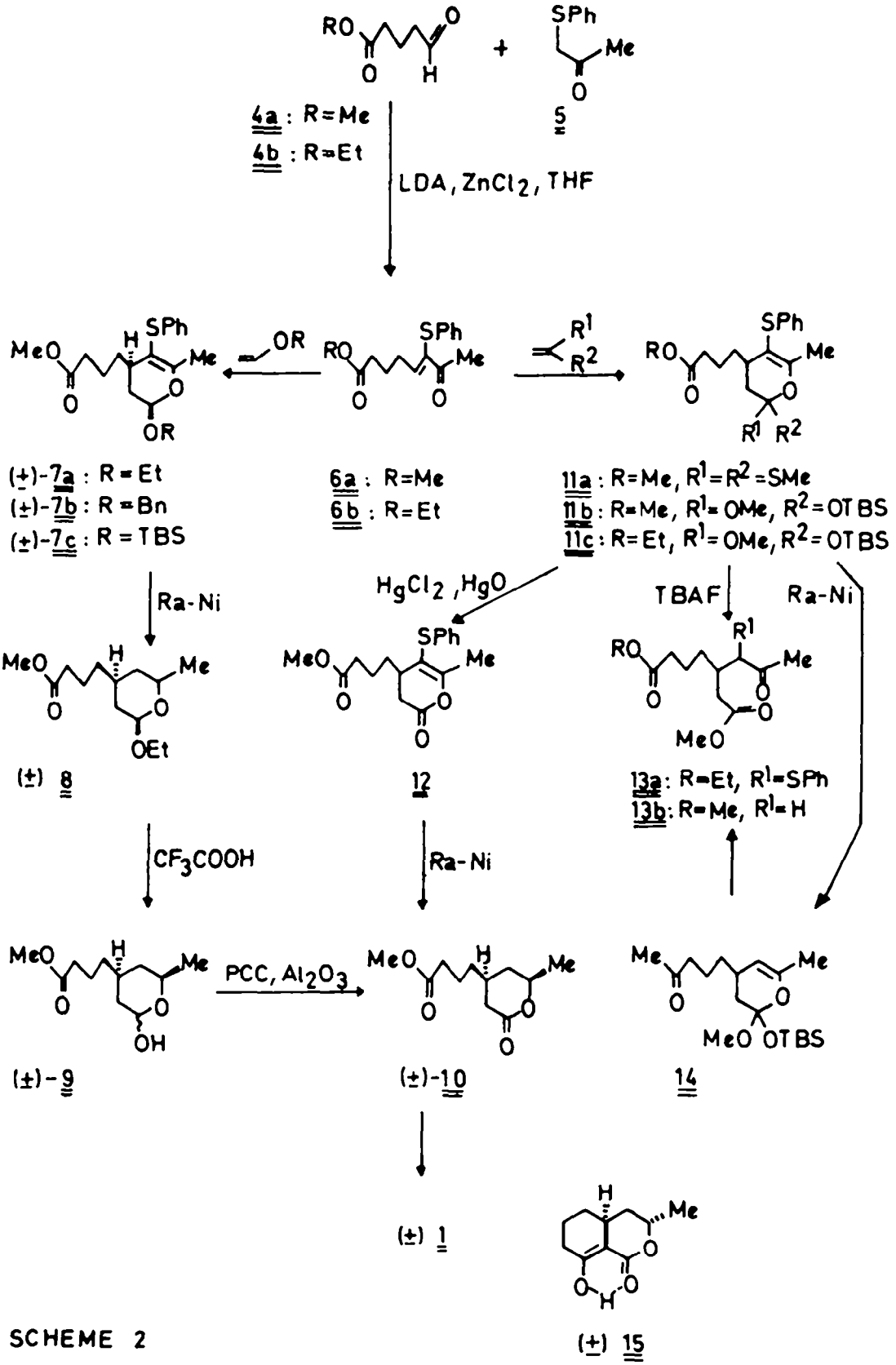
SCHEME 1

As outlined in the retrosynthetic Scheme 1 the required 1-oxa-1,3-diene precursor B should be readily available from a 4-formylbutanoate derivative 4 and phenylthioacetone (5). Hetero-Diels-Alder reaction with enol ether or ketene acetal derivatives should provide the desired dihydropyran intermediate A which after diastereoselective CC-double bond transformation and chemoselective ring closure yields the target molecule.

RESULTS AND DISCUSSION

The required 1-oxa-1,3-diene precursors 6a and 6b (Scheme 2) were synthesized according to the synthesis design (Scheme 1) from phenylthioacetone (5) [22] and methyl or ethyl 4-formyl butanoate (4a,b); compounds 4a,b were readily obtained via ozonolysis of cyclopentene using a procedure of Schreiber, Claus, and Reagan. [23] The condensation was carried out with lithium diisopropylamide (LDA) in presence of zinc chloride according to Hoye and Kurth [24] affording compounds 6a,b in good yields as Z-isomers. [5,25]

Cycloaddition reaction of compound 6a with ethyl and with benzyl vinyl ether was performed because of reactivity [26] under high pressure (5 kbar); it furnished exclusively the endo-isomers (±)-7a and (±)-7b, respectively. However, the sterically demanding tert.-butyldimethylsilyl (TBS) vinyl ether [27] provided a 3:1 endo/exo-mixture of the cycloadduct (±)-7c. The structures could be assigned by comparison of the ^{1}H-n.m.r. data with previous results. [5] Raney nickel treatment of compound (±)-7a in refluxing ethanol yielded in one step via phenylthio group removal and site selective hydrogen transfer the desired tetrahydropyran derivative (±)-8 in a favorable 6:1 cis/trans ratio. Glycoside bond cleavage with trifluoroacetic acid/water furnished a mixture from which the cis isomer (±)-9 (anomeric mixture) was separated. This compound was oxidized with pyridinium chlo-


RO
O
O
H
+
SPh
Me
O
4a : R=Me
4b : R=Et
5
LDA, ZnCl2, THF
MeO
H
SPh
Me
O
OR
OR
RO
SPh
Me
O
O
R1
R2
RO
SPh
Me
O
O
R1 R2
(±)-7a : R = Et
(±)-7b : R = Bn
(±)-7c : R = TBS
6a : R=Me
6b : R=Et
11a : R=Me, R1=R2=SMe
11b : R=Me, R1=OMe, R2=OTBS
11c : R=Et, R1=OMe, R2=OTBS
Ra-Ni
HgCl2, HgO
TBAF
Ra-Ni
MeO
H
Me
O
O
OEt
MeO
SPh
Me
O
O
O
RO
R1
Me
O
O
MeO
(±) 8
12
13a : R=Et, R1=SPh
13b : R=Me, R1=H
CF3COOH
Ra-Ni
MeO
H
Me
O
O
OH
PCC, Al2O3
MeO
H
Me
O
O
O
Me
Me
O
O
MeO OTBS
(±)-9
(±)-10
14
(±) 1
H
Me
O
O
O
H
(±) 15

SCHEME 2

rochromate (PCC) on aluminum oxide in benzene in presence of molecular sieves [28] to yield the δ-lactone (±)-10 which by treatment with potassium tert.-butoxide in tetrahydrofuran was readily cyclized to the desired ramulosin (±)-1; its structure was assigned by comparison with published physical data. [29]

Obviously, in this synthetic strategy cycloaddition of ketene acetals as heterodienophiles to the 1-oxa-1,3-dienes 6a,b should permit a shorter route to (±)-ramulosin, because at least oxidation to the lactone stage would not be required. Correspondingly, compound 6a was treated with 1,1-bismethylthio-ethylene [30] under high pressure (5 kbar) affording the dihydropyran cycloadduct 11a in good yield. 1-tert.-Butyldimethylsilyloxy-1-methoxyethylene [31] reacted already under normal pressure with compounds 6a,b providing the corresponding dihydropyrans 11b,c, respectively, in quantitative yields (7:3 diastereomer mixture). However, desilylation for instance of compound 11c with tetrabutylammonium fluoride (TBAF), to obtain directly the lactone 12 (ethyl ester) or in one step due to the basicity of TBAF the subsequent ring cyclized product, resulted only in dihydropyran ring opening furnishing diester 13a. Therefore removal of the phenylthio group with Raney nickel from compound 11b, providing readily dihydropyran 14, and subsequent hydrogenation was investigated. But all attempts to transfer hydrogen to compound 14 resulted in preferred ring cleavage furnishing the diester 13b.

However, transformation of compound 11a into lactone 12 was readily accomplished with $HgO/HgCl_2$ in acetone/water. [32] Treatment of this compound with Raney nickel under 4 bar hydrogen pressure led again in one step to phenylthio group removal and subsequent site-selective hydrogen transfer providing δ-lactone (±)-10 in a favorable 7:1 cis/trans-ratio from which the minor isomer could be separated. Cyclization of the cis/trans-mixture under the conditions described above afforded ramulosin (±)-1 and epiramulosin (±)-15, which was separated and identified by comparison with published physical data. [29]

EXPERIMENTAL

General Procedures

Petroleum ether 40°-65° was used, if not otherwise indicated. - R_F values refer to t.l.c. performed on silica gel (Merck) with the solvent systems noted. - Column chromatography was performed under medium pressure with silica gel (Merck, "LiChroprep" Si60, 40-60 μm) and by flash chromatography with silica gel(Merck, 230-400 mesh). - Melting points are uncorrected. - ^{1}H-N.m.r. spectra were recorded in the solvent systems noted (Me_4Si, 0.00 ppm) with a Bruker 250 Cryospec.

Ethyl 7-oxo-6-phenylthio-5-octenoate 6b

To a solution of 45.5 mmol lithium diisopropylamide (LDA) in 120 ml dry tetrahydrofuran is added at -80°C and under nitrogen a solution of 7.55 g (45.5 mmol) 1-phenylthio-2-propanone [22] (5) in 10 ml dry tetrahydrofuran. After 30 min a solution of 9.54 g (70.0 mmol) $ZnCl_2$ in 100 ml dry tetrahydrofuran is introduced, then the temperature of the mixture is raised to -20°C and a solution of 7.92 g (55.0 mmol) ethyl 4-formylbutanoate [23] (4b) in 10 ml dry tetrahydrofuran added. After 30 min the reaction mixture is warmed to 0°C and kept for 30 min at this temperature. The reaction mixture is treated with saturated ammonium chloride solution and then extracted with ether. The organic phase is separated, washed with water, dried over anhydrous magnesium sulfate and evaporated. The oily residue was purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 4:1) to yield 10.23 g (77 %) of 6b as a colourless oil. - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.34; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.0 Hz, 3H, OCH_2-CH_3), 1.85 (tt, $J_{2,3} = J_{3,4}$ = 7.5 Hz, 2H, 3-H), 2.28 (s, 3H, 8-H), 2.38 (t, J = 7.5 Hz, 2H, 2-H), 2.56 (dt, $J_{3,4} = J_{4,5}$ = 7.5 Hz, 2H, 4-H), 4.12 (q,

J = 7.0 Hz, 2H, O-C<u>H</u>$_2$-CH$_3$), 7.13-7.29 (m, 6H, C_6H_5, 5-H). - Found: C, 65.51; H, 6.93. Calc. for $C_{16}H_{20}O_3S$: C, 65.73; H, 6.89.

Methyl 7-oxo-6-phenylthio-5-octenoate 6a

This compound is obtained from 5 and methyl 4-formylbutanoate [23] (4a) as described for 6b. It was used without further characterization in the subsequent steps. - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.33.

Methyl 4-(r-2'-ethoxy-6'-methyl-5'-phenylthio-3',4'-dihydro-2'H-pyran-c-4'-yl)butanoate (±)-7a

A solution of 4.40 g (15.8 mmol) 6a and 20 mg hydroquinone in 10 ml ethyl vinyl ether is kept at 70°C and 5 kbar for 48 h. The reaction mixture is concentrated and the oily residue purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 8:1) to yield 5.55 g (qu) of (±)-7a as colourless oil. - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.56; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ = 1.22-1.28 (t, J = 7.1 Hz, 3H, O-CH$_2$-C<u>H</u>$_3$), 2.08 (d, J = 1.5 Hz, 3H, 6'-C-CH$_3$), 1.40-2.10 (m, 7H, 3-CH$_2$, 4-CH$_2$, 4'-CH), 2.20-2.25 (m, 2H, 2-H), 3.62 (s, 3H, -COOCH$_3$), 3.53-3.65 (m, 1H, -O-C<u>H</u>-CH$_3$), 3.86-3.95 (m, 1H, O-C<u>H</u>-CH$_3$), 5.07 (dd, $J_{2',3'}$ = 6.0, $J_{2',3''}$ = 2.5 Hz, 1H, 2'-CH), 7.06-7.28 (m, 5H, C_6H_5). - Found: C, 64.91; H, 7.56. Calc. for $C_{19}H_{26}O_4S$: C, 65.11; H, 7.48.

Methyl 4-(r-2'-benzyloxy-6'-methyl-5'-phenylthio-3',4'-dihydro-2'H-pyran-c-4'-yl)butanoate (±)-7b

A solution of 4.00 g (14.4 mmol) 6a and 20 mg hydroquinone in 5 ml benzyl vinyl ether is kept at 60°C and 5 kbar for 48 h. The reaction mixture is purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 8:1) to yield 5.90 g (qu) of ±)-7b as a slightly yellowish oil. - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.48; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ = 1.38-1.90 (m, 4H, 3-CH$_2$, 4-CH$_2$), 1.95-2.10 (m, 2H, 3'-CH$_2$), 2.06 (d, J = 1.2 Hz, 3H, 6'-C-CH$_3$), 2.12-2.31 (m, 3H, 2-CH$_2$, 4'-CH), 3.59 (s, 3H, COOCH$_3$), 4.63 and 4.89 (2d, J = 12.1 Hz, C<u>H</u>$_2$-C_6H_5), 5.19 (dd, $J_{2',3'}$ =3.1, $J_{2',3''}$ = 4.6 Hz, 1H, 2'-CH), 7.05-7.41 (m, 10H, 2 C_6H_5). - Found: C, 69.88; H, 6.62. Calc. for $C_{24}H_{28}O_4S$: C, 69.87; H, 6.84.

Methyl 4-(2'-tert.-butyldimethylsilyloxy-6'-methyl-5'-phenylthio-3',4'-dihydro-2'-H-pyran-4'-yl)butanoate (±)-7c

A solution of 2.60 g (9.3 mmol) 6a, 3.16 g (20 mmol) tert.-butyldimethylsilyl vinyl ether [27], and 20 mg hydroquinone is kept at 70°C and 5 kbar for 48 h. Excess vinyl ether is then removed under reduced pressure and the oily residue purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 10:1) to yield 3.00 g (74 %) of (±)-7c as colourless oil. ^{1}H-N.m.r. indicated a 3:1 endo:exo-mixture. - T.l.c. (petroleum ether :ethyl acetate, 4:1) R_F 0.67; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ = 0.15, 0.16, 0.17 (3s, 6H, Si(CH$_3$)$_2$), 0.92, 0.95 (2s, 9H, Si-t-Bu), 1.22-2.02 (m, 6H, 3-CH$_2$, 4-CH$_2$, 3'-CH$_2$), 2.04 (d, J = 1.2 Hz, 3H, 6'-C-CH$_3$), 2.14-2.29 (m, 3H, 2-CH$_2$, 4'-CH), 3.61, 3.63 (2s, 3H, -COOCH$_3$), 5.40-5.44 (m, 1H, 2'-CH), 7.05-7.24 (m, 5H, C_6H_5). - Found: C, 63.12; H, 8.33. Calc. for $C_{23}H_{36}O_4S$ Si: C, 63.26; H, 8.31.

Methyl 4-(r-2'-ethoxy-6'-methyl-tetrahydropyran-c-4'-yl)-butanoate (±)-8

To a solution of 4.25 g (12.1 mmol) (±)-7a in 20 ml dry ethanol is added excess Raney-nickel (W2). The mixture is heated to reflux for 1 h, the solvent is decanted and the solod residue washed with ethyl acetate. The organic solutions are combined, concentrated and the oily residue purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 8:1) to yield 1.92 g (65 %) of (±)-8 as colourless oil. ^{1}H-n.m.r. indicated a 6:1 ratio of c-6'-methyl : t-6'-methyl mixture, which could not be separated. This material was used in the next step. - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.48; - ^{1}H-n.m.r. (250 MHz,

$CDCl_3$) δ = 0.79-1.38 (m, 10H, 4-CH_2, 5'-CH_2, 6'-C-CH_3, O-CH_2-CH_3), 1.50-1.89 (m, 5H, 3'-CH_2, 4'-CH, 3-CH_2), 2.27-2.33 (t, J = 7.4 Hz, 2H, 2-CH_2), 3.45-3.58 (m, 2H, 6'-CH, -O-CH-CH_3), 3.67 (s, 3H, $COOCH_3$), 3.89 (m, 1H, O-CH-CH_3), 4.39 (dd, $J_{2',3'a}$ = 9.6, $J_{2',3'e}$ = 2.0 Hz, 0.86 H, 2'-CH of c-6'-methyl isomer), 4.64 (dd, $J_{2',3'a}$ = 9.6, $J_{2',3e'}$ = 2.0 Hz, 0.14 H, 2'-CH of t-6'-methyl isomer).

Methyl 4-(2'-hydroxy-c-6'-methyl-tetrahydropyran-r-4'-yl)butanoate (±)-9

A solution of 0.73 g (3 mmol) (±)-8 (6:1-mixture) in 20 ml tetrahydrofuran was treated with 1 ml trifluoroacetic acid in water (1:10) for 2 h at room temperature. The reaction mixture is concentrated under reduced pressure, treated with toluene and again concentrated. The residue is purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 7:3) to yield a colourless solid material which crystallizes from cyclohexane. Separation of the major isomer (±)-9 is accomplished by medium pressure chromatography (silica gel, petroleum ether : ethyl acetate, 7:3), to yield 0.41 g (64 %) of (±)-9 as colourless solid material (anomeric mixture). - T.l.c. (petroleum ether : ethyl acetate, 1:1) R_F 0.38 (and 0.42 for the minor isomer); - ^{1}H-n.m.r. (250 MHz, CDCl3): δ = 0.78-1.33, 1.51-1.99 (2m, 12H, 3-CH_2, 4-CH_2, 3'-CH_2, 4'-CH, 5'-CH_2, 6'-C-CH_3), 2.31 (t, J = 7.5 Hz, 2H, 2-CH_2), 3.18 (bs, 0.43H, α-2'-OH), 3.49-3.64 (m, 0.57H, β-6'-CH), 3.67 (2s, 3H, $COOCH_3$), 3.80 (d, $J_{2',OH}$ = 6.2 Hz, 0.57H, β-2'-OH), 4.02-4.18 (m, 0.43H, α-6'-CH), 4.74 (ddd, $J_{2',3'}$ = 2.1 and 8.5 Hz, $J_{2'-OH}$ = 6.2 Hz, 0.57H, β-2'-CH), 5.34 (bs, 0.43H, α-2'-CH). - Found: C, 60.90; H, 9.08. Calc. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32.

Methyl 4-(c-6'-methyl-tetrahydropyran-2'-on-r-4'-yl)-butanoate (±)-10

(a) From (±)-9:

To a solution of 0.60 g (2.8 mmol) of (±)-9 in 10 ml dry benzene is added 1.5 g ground molecular sieves (4 Å) and 6 g (≈ 6 mmol) pyridinium chlorochromate on Al_2O_3 [28] at room temperature. The reaction mixture is filtered after 5 h, the residual oxidizing agent is treated several times with ether, the organic solutions are combined and treated with florisil for crude purification. The resulting material is purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 7:3) to yield 0.33 g (55 %) of (±)-10 as solid material. - T.l.c. (petroleum ether : ethyl acetate, 7:3) R_F 0.24; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 1.12-1.27 (m, 1H, 5'-CH), 1.30-1.39 (m, 2H, H-CH_2), 1.37 (d, J = 6.1 Hz, 3H, 6'-C-CH_3), 1.59-1.73 (m, 2H, 3-CH_2), 1.88-2.14 (m, 3H, 3'-CH_a, 4'-CH, 5'-CH_e), 2.32 (t, J = 7.3 Hz, 2H, 2-CH_2), 2.70 (ddd, $J_{3',3'}$ = 17, $J_{3',4'}$ = 1.8 Hz, 1H, 3'-CH_e), 3.68 (s, 3H, $COOCH_3$), 4.33-4.47 (ddq, $J_{6',CH3}$ = 6.1, $J_{6',5'a}$ = 12.4, $J_{6',5'e}$ = 2.4 Hz, 1H, 6'-CH). - Found: C, 61.62; H, 8.45. Calc. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47.

(b) From 12:

A solution of 0.38 g (1.2 mmol) of 12 in 10 ml ethyl acetate was treated for 7 h with Raney-nickel (W-2) and hydrogen at 4 bar. The solvent is decanted and the Raney-nickel washed several times with ethyl acetate. The ethyl acetate solutions are combined, concentrated and the residue purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 7:3) to yield 0.21 g (82 %) of a 7:1 mixture of (±)-10 and the trans-isomer, respectively, which can be separated by medium pressure chromatography (silica gel, petroleum ether : ethyl acetate, 7:3).

Methyl 4-(2,2'-bismethylthio-6'-methyl-5'-phenylthio-3',4'-dihydro-2'H-pyran-4'-yl)butanoate 11a

A solution of 2.20 g (7.9 mmol) of 6a, 1.50 g (12.5 mmol) 1.1-Bismethylthioethylene [30] and 20 mg hydroquinone in 5 ml dry dioxane is kept at 70°C and 5 kbar for 48 h. The reaction mixture is concentrated and the oily residue purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 8:1) to yield 2.27 g (72 %) of 11a as colourless oil. - T.l.c. (petroleum ether : ethyl acetate, 8:1) R_F 0.38; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 1.28-1.70 (m, 3H, 4-CH_2, 3-CH), 1.83-1.94 (m, 1H, 3-CH), 2.10 (d, J = 1.8 Hz, 3H, 6'-C-CH_3), 2.17-2.28 (m, 3H, 2-CH_2, 3'-CH_a), 2.20, 2.25 (2s, 6H, 2 SCH_3), 2.37 (dd, $J_{3',4'}$ = 6.4, $J_{3'a,3'e}$ = 14 Hz, 1H, 3'-CH_e), 2.53-2.60 (m, 1H, 4'-CH), 3.63 (s, 3H, $COOCH_3$), 7.06-7.32 (m, 5H, C_6H_5). - Found: C, 56.85; H, 6.53. Calc. for $C_{19}H_{26}O_3S_3$: C, 57.25; H, 6.57.

Ethyl 4-(2'-tert.-butyldimethylsilyloxy-2'-methoxy-6'-methyl-5'-phenylthio-3',4'-dihydro-2'H-pyran-4-yl)-butanoate 11c

A solution of 1.99 g (6.8 mmol) 6b and 2.0 g (10.6 mmol) 1-tert.-butyldimethylsilyloxy-1-methoxyethylene [31] is stirred for 2 d at room temperature and then for 12 h at 50°C. The reaction mixture is purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 12:1) to yield 3.26 g (qu) of 11b as colourless oil. (^{1}H-n.m.r. indicates a 7:3 mixture of diastereoisomers, which was not separated). - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.73; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 0.17, 0.18, 0.22, 0.23 (4s, 6H, $Si(CH_3)_2$), 0.93, 0.94 (2s, 9H, Sit-Bu), 1.22 (t, J = 7.1 Hz, 3H, O-CH_2-CH_3), 1.35-1.80 (m, 4H, 3-CH_2, 4-CH_2), 1.89-2.05 (m, 2H, 3'-CH_2), 2.08 (d, J = 1.8 Hz, 3H, 6'-C-CH_3), 2.19-2.26 (m, 3H, 2-CH_2, 4'-CH), 3.33, 3.36 (2s, 3H, OCH_3), 4.03-4.12 (m, 2H, O-CH_2-CH_3), 7.06-7.26 (m, 5H, C_6H_5). - Found: C, 62.46; H, 8.39. Calc. for $C_{25}H_{40}O_5SSi$: C, 62.49; H, 8.53.

Methyl 4-(2'-tert.-butyldimethylsilyloxy-2'-methoxy-6'-methyl-5'-phenylthio-3',4'-dihydro-2'H-pyran-4'-yl)butanoate 11b

This compound is obtained from 6a and 1-tert.-butyldimethylsilyloxy-1-methoxyethylene [29] as described for compound 11c. (It was used directly in the transformation to compound 14). - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.72.

Methyl 4-(6'-methyl-5'-phenylthio-3',4'-dihydro-2'H-pyran-2'-on-4'-yl)butanoate 12

To a solution of 1.40 g (3.5 mmol) 11a in 20 ml acetone/water (10:1) is added 1.90 g (7 mmol) $HgCl_2$ and 1.50 g (7 mmol) HgO under vigorous stirring at room temperature. The reaction mixture is filtered after 10 min, the solid residue extracted with ether, and the combined organic solutions washed with water and dried over anhydrous $MgSO_4$. Concentration of this solution provides a practically pure material, which can be made analytically pure by medium pressure chromatography (silica gel, petroleum ether : ethyl acetate, 4:1). Yield 1.12 g (qu) of 12 as colourless oil. - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.35; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 1.21-1.74 (m, 4H, 3-CH_2, 4-CH_2), 2.21 (d, J = 0.9 Hz, 3H, 6'-C-CH_3), 2.26 (t, J = 7.0 Hz, 2H, 2-CH_2), 2.33-2.38 (m, 1H, 4'-CH), 2.63-2.76 (m, 2H, 3'-CH_2), 3.65 (s, 3H, $COOCH_3$), 7.17-7.35 (m, 5H, C_6H_5). - Found: C, 63.52; H, 6.42. Calc. for $C_{17}H_{20}O_4S$: C, 63.72; H, 6.29.

Ethyl methyl 3-(2-oxo-1-phenylthio-propyl)heptanedioate 13a

A solution of 1.20 g (2.5 mmol) 11b in 20 ml dry tetrahydrofuran is cooled under nitrogen atmosphere to -20°C and then 0.80 g (2.5 mmol) tetrabutyl ammonium fluoride x $3H_2O$ is added. The reaction mixture is extracted after 10 min with ether/saturated NaCl-solution. The organic phase is dried over anhydrous $MgSO_4$, and concentrated. The oily residue is purified by flash chromatography (silica

gel, petroleum ether : ethyl acetate, 4:1) to yield 0.74 g (80 %) of 13a as colourless oil. - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.32; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 1.21-1.29 (m, 3H, O-CH_2-CH_3), 1.38-1.82, 2.17-2.86 (2m, 9H), 2.26, 2.28 (2s, 3H, CO-CH_3), 3.66, 3.69 (2s, 3H, $COOCH_3$), 3.78, 3.89 (2d, J = 8.5 Hz, 1H, CH-SC_6H_5), 4.06-4.17 (m, 2H, $COOCH_2$-CH_3), 7.28-7.42 (m, 5H, C_6H_5). - Found: C, 62.13; H, 7.10. Calc. for $C_{19}H_{26}O_5S$: C, 62.27; H, 7.15.

Dimethyl 3-(2-oxopropyl)heptanedioate 13b

A solution of 0.70 g (1.95 mmol) 14 in 5 ml methanol is treated with hydrogen in presence of palladium on carbon for 2 h. The reaction mixture is filtered, the filtrate washed with methanol, and the methanol solutions concentrated. The oily residue is purified by flash chromatography (silica gel, petroleum ether : ethyl acetate, 4:1) to yield 0.41 g (86 %) of 13b as colourless oil. - T.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.22; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 1.30-1.39 (m, 2H, 4-CH_2), 1.56-1.68 (m, 2H, 5-CH_2), 2.14 (s, 3H, $COCH_3$), 2.26-2.37 (m, 4H, 2-CH_2, 6-CH_2), 2.37-2.45 (m, 1H, 3-CH), 2.48-2.52 (m, 2H, CO-CH_2), 3.66, 3.67 (2s, 6H, 2-$COOCH_3$). - Found: C, 59.06; H, 8.21. Calc. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25.

Mehtyl 4-(2'-tert.-butyldimethylsilyloxy-2'-methoxy-6'-methyl-3',4'-dihydro-2'-H-pyran-4'-yl)butanoate 14

A solution of 1.00 g (2.1 mmol) 11c (7:3 mixture of the obtained diastereoisomers) in 10 ml ethanol is treated with Raney-nickel (W-2) in presence of hydrogen at room temperature. The reaction mixture is filtered after 2 h and the filtrate washed several times with ethanol. Evaporation of the ethanol provides a practically pure product which is purified for analytical purposes by medium pressure chromatography (silica gel, petroleum ether : ethyl acetate, 12:1). Yield 0.70 g (92 %) of 14 as colourless oil. - (^{1}H-n.m.r. indicates a 7:3 mixture of diastereomers, which was not separated). - T.l.c. (petroleum ether : ethyl acetate, 8:1) R_F 0.53; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 0.11, 0.18, 0.20 (3s, 6H, $Si(CH_3)_2$), 0.88, 0.99 (2s, 9H, Sit-Bu), 1.22-2.10 (m, 6H, 3-CH_2, 4-CH_2, 3'-CH_2), 1.73 (dd, $J_{5',CH2}$ = 0.9; $J_{4',CH3}$ = 0.9 Hz, 3H, 6'-C-CH_3), 2.18-2.32 (m, 1H, 4'-CH), 2.27-2.34 (t, $J_{2,3}$ = 7.6 Hz, 2H, 2-CH_2), 3.27, 3.31 (2s, 3H, OCH_3), 3.67 (s, 3H, $COOCH_3$), 4.46 (bs, 1H, 5'-CH).

(±)-Ramulosin (±)-1

A solution of 0.20 g (0.90 mmol) (±)-10 in 10 ml dry tetrahydrofuran is treated with excess potassium tert.-butoxide (freshly sublimed) at room temperature. After stirring for 15 min the reaction mixture is extracted with ether/water. The ether extract is washed with water, concentrated and the residue purified by medium pressure chromatography (silica gel, petroleum ether, ethyl acetate, 4:1) to yield 0.14 g (83 %) of (±)-1 as solid material, which crystallized from petroleum ether (b.p. 80-100°) m.p. 114° (ref. [16] 115°; ref. [13] 120°). - T.l.c. (petroleum ether; ethyl acetate, 4:1) R_F 0.42; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 1.08-1.34 (m, 2H, H-H_a, 5-H_a), 1.38 (d, J = 6.4 Hz, 3H, 3-CH_3), 1.55-1.74 (m, 1H, 6-H_a), 1.84-1.94 (m, 2H, 5-H_e, 6-H_e), 1.95-1.98 (dd, $J_{4e,3}$ = 2.4, $J_{4e,4a}$ = 3.9 Hz, 1H, 4-H_e), 2.34-2.41 (m, 2H, 27-H), 2.44-2.57 (m, 1H, 4a-H), 4.39-4.53 (ddq, $J_{3,4e}$ = 2.4, $J_{3,4a}$ = 12.8, $J_{3,CH3}$ = 6.4 Hz, 1H, 3-H), 13.26 (s, 1H, OH).

(±)-epi-Ramulosin (±)-15

When a solution of (±)-10 containing the corresponding trans-isomer is treated as described for the preparation of (±)-1, a mixture of (±)-1 and (±)-15 is obtained which is separated by medium pressure chromatography (silica gel, petroleum ether : ethyl acetate, 4:1). Yield: 71 % (±)-1 and 12 % (±)-15.

(±)-15: M.p. 64°; ref. 15 64-65°C; - t.l.c. (petroleum ether : ethyl acetate, 4:1) R_F 0.40; - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ = 1.11-1.34 (m, 1H, 5-H_a), 1.40 (d,

J = 6.7 Hz, 3H, 3-CH_3), 1.60-2.00 (m, 5H, 4-H_a, 4-H_e, 5-H_e, 6-H_a, 6-H_e), 2.36-2.43 (m, 2H, 7-H_a, 7-H_e), 2.61-2.67 (m, 1H, 4a-H), 4.73-4.79 (m, 1H, 3-H), 13.35 (s, 1H, OH). - These data coincide with published data [15].

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