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An Efficient Synthesis of Radicinin Analogues

[a]Marcus Eh, [b]Dietmar Schomburg, [b]Kathrin Schicht, [a]Markus Kalesse*

[a]Institut für Organische Chemie der Universität Hannover, Schneiderberg 1b, D-30167 Hannover; (Germany)
[b]Gesellschaft für Biotechnologische Forschung, Abteilung: „Molekulare Strukturforschung", Maschenroder Weg 1, D-38108 Braunschweig; (Germany)

Abstract: We describe herein an enantio- and diastereoselective total synthesis of two radicinin analogues **13** and **14**. **13** has been subjected to biological tests, exhibiting the lowest toxicity of all radicinin analogues that have been investigated to date and it depresses the heart ventricular strip and histamine contraction. The key reaction to establish the radicinin skeleton is the reduction of the pseudo C_2 symmetrical precursor **11** with the aid of $TiCl_4$ and $LiBH_4$.

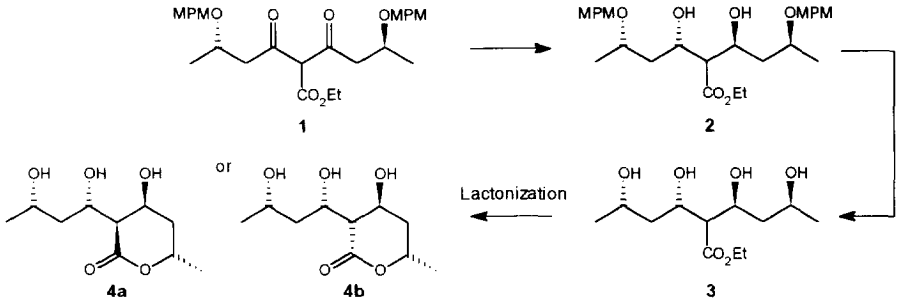
Introduction

It has been long known that radicinin and radicinin analogues exhibit antimicrobial and antifungal activity.[1] Although radicinin analogues had been synthesized by hydrogenation of aromatic precursors,[2] there has been no enantio and diastereoselective total synthesis of the radicinin analogues **13** and **14** to date. The hydrogenation method does not yield homochiral compounds, nor can one change selectively the configuration in a distinct manner at selected carbon atoms. In our efforts to establish an efficient and configurationally flexible strategy for the sequential two directional chain synthesis to synthesize macrolide antibiotics, we observed a unique reduction that leads to tetra-substituted tetrahydropyran moieties. This reduction, followed by subsequent lactonization and hydrogenation, yields **14** in good quantities. The described sequence enables us to perform the first total synthesis of the homochiral radicinin metabolites **13** and **14**.

Results and Discussion

The principal idea for the original route towards two-directional chain extension[3] was to generate pseudo C_2 symmetric bis-ketoester **1**, which can be reduced to pseudo C_2 symmetric tetraol **3** by chelation-controlled reduction with borohydrides.[4] Tetraol **3** should be subjected to intra-molecular transesterification in order to achieve side chain differentiation[5] (Scheme 1).

Scheme 1

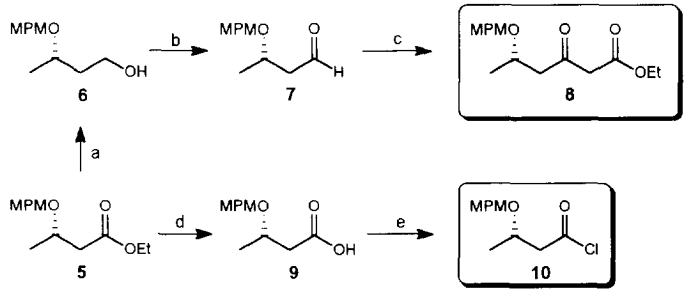


Synthetic strategy for the sequential two-directional chain extension and terminus differentiation.

By using various Lewis acids as the chelating agents in the reduction step, we discovered a unique reaction sequence. When $TiCl_4$ was used as the chelating agent, reduction of just one of the two keto groups was observed and an additional ring closure occurred. This reaction sequence established the tetrahydropyran moiety of the final product (**13**, **14**) in a straightforward manner.

A readily available starting material for 3-hydroxybutanoate is ethyl acetoacetate.[6] Reduction with baker's yeast generates (S)-(+)-ethyl hydroxy butanoate in 61% yield and with 90% enantiomeric excess.[7] Protection of the hydroxy group with MPM trichloroacetimidate yields the MPM protected β-hydroxyester **5** in 85 % yield.[8]

Scheme 2

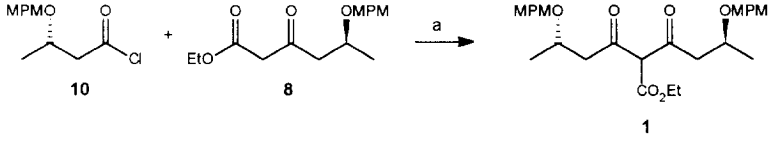


a) LAH, Et_2O, RT, 85%; b) Swern Oxidation, 47%; c) Ethyl diazoacetate, $SnCl_2$, CH_2Cl_2, 64%; d) LiOH, $MeOH/H_2O$ = 3:1, 88%; e) $SOCl_2$, cyclohexane, crude.

Ester **5** was subjected to LAH reduction and then oxidized via Swern oxidation.[9] The generated aldehyde was converted to the β-keto ester **8** by treatment with ethyl diazoacetate and anhydrous tin dichloride.[10] The

acid chloride **10**, used in the subsequent $MgCl_2$ mediated coupling,[11] was generated by LiOH hydrolysis[12] of the ester, followed by acid chloride generation with the aid of thionyl chloride in cyclohexane (Scheme 2). It is crucial to avoid the use of any base or even DMF as a catalyst. We found that even catalytic amounts of DMF, which is very often used in acid chloride formation,[13] facilitate the elimination of the MPM-protected hydroxy group. The crude acid chloride **10** was then coupled to keto ester **8** with $MgCl_2$ as the chelating agent and with pyridine as base (Scheme 3).

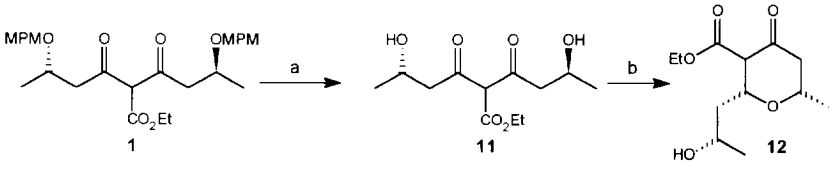
Scheme 3



a) $MgCl_2$, pyridine, CH_2Cl_2, 61%.

The so-generated pseudo C_2 symmetric diketone **1** was deprotected with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) according to standard procedures[14] and subjected to various chelation-controlled reductions[4] (Scheme 4). Chelating boron reagents lead to difficulties in tetraol liberation. We therefore examined various different Lewis acids for chelation of the two β-hydroxy ketones. Investigation of a great variety of hydride sources left $TiCl_4$ and $LiBH_4$ as the superior system. Surprisingly, just one carbonyl group was reduced and consecutive ring closure took place.

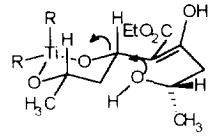
Scheme 4



a) DDQ, CH_2Cl_2/H_2O = 18:1, 59%; b) $TiCl_4$, THF/MeOH = 5:1, $LiBH_4$, 77%.

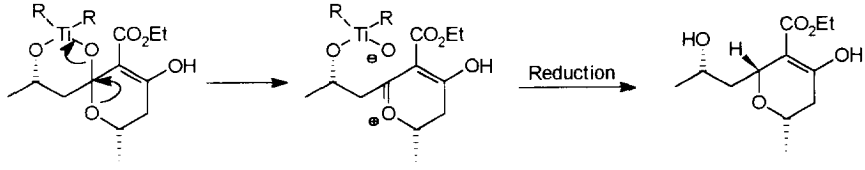
This product may derive via a reduction-S_N2 mechanism (Scheme 5a) or via hemiacetal formation, elimination and succeeding reduction of the oxonium ion (Scheme 5b). The reaction proceeds diastereoselectively and the other diastereomer could not be observed.

Scheme 5a



Model for the S_N2-reaction; R=Methoxide.

Scheme 5b

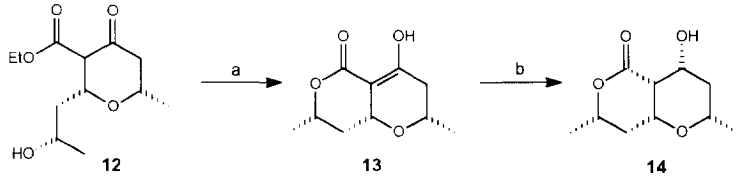


Elimination-reduction model.

The configuration at the newly-generated asymmetric ether carbon atom is consistent with a syn-reduction followed by S_N2 displacement. On the other hand, hemiacetal formation, elimination and succeeding reduction would yield compound **12**, too.

Since compound **11** is pseudo C_2 symmetric prior to reduction, it makes no difference which of the two carbonyl groups is reduced. Catalytic hydrogenation of the enol as the final step generates the desired stereochemistry by means of the concave/convex geometry of lactone **13** (Scheme 6).

Scheme 6



a)TFA, CH_2Cl_2, 56%, b) H_2, Pd/C, 40°C, 3 bar, 81%.

Lactonization of tetrahydropyran **12** generated the radicinin analogue **13,** which was subjected to X-ray crystallography (Figure 1). The X-ray structure[15] shows compound **13** as a rather flat bicyclic system with the highest deviation from the planes occurring at O(16) (36pm) and C(24). A strong intramolecular hydrogen bond is observed between O(32)H and O(33) (H...O distance 158 pm). The data elucidated the stereochemistry of **13** and revealed the orientation of the substituents. Hydrogenation of **13** at 3 bar and 40°C afforded **14** in 81% yield. The stereochemistry of compound **14** was confirmed by NOE experiments.

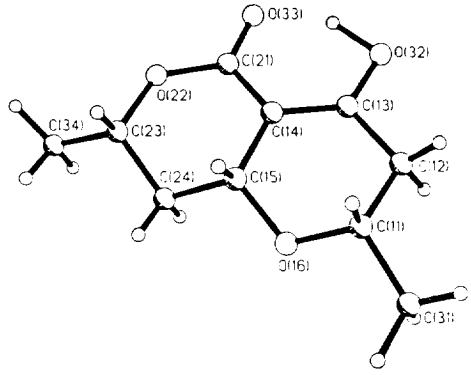


Figure 1. Molecular structure of compound **13**: C-C bonds 144-152 pm, C-O 135-147 pm, C=O bond 123 pm, C=C bond 134 pm.

This short and efficient route establishes the synthesis of two radicinin metabolites in eight consecutive steps and generates five asymmetric centers by using the same chiral starting material (S-(+)-ethyl hydroxybutanoate) for both parts of the molecule. The sequential two-directional chain extension strategy provided us with the required ketone for our short synthesis of homochiral radicinin analogues.

These compounds are presently undergoing pharmacological testing.

Experimental Section

General. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker WP 200 or AM 300 spectrometer. Proton NMR splitting patterns are designated as: br, broad; s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. Coupling constants are reported in hertz (Hz). Infrared (IR) spectra were recorded on a Perkin Elmer FT 1710 spectrometer. Mass spectra (MS) were recorded on a Finnigan MAT 312 mass spectrometer at an ionization potential of 70 eV. High resolution mass spectra (HRMS) were recorded on an VG Autospec mass spectrometer at an ionization potential of 70 eV. Elemental analyses were performed on a Heraeus CHN Rapid analyser. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Flash chromatography was performed with Baker Flash silica gel (0.03-0.04 mm). Merck TLC 60 F 254 thin layer chromatography (TLC) plates were used.

All solvents were distilled prior to use. Anhydrous reactions were performed under an atmosphere of nitrogen in flame-dried (under vacuum) glassware.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium immediately before use. Dichloromethane (CH_2Cl_2) and dimethylsulfoxide (DMSO) were distilled from CaH_2.

(2S,8S)-4,6-Oxo-5-carboxyethyl-2,8-[(p-methoxybenzyl)-oxy]-nonane (1): To a solution of 324 mg (3.4 mmol) dry magnesium chloride in 5.5 ml CH_2Cl_2 was added 1.0 g (3.4 mmol) of the β-ketoester **8**. The reaction mixture was cooled to 0°C and a first equivalent of pyridine (275 µl, 3.4 mmol) was added. The resulting heterogeneous mixture was stirred for 1 h at 0°C, followed by the addition of the acid chloride, dissolved in 3.3 ml CH_2Cl_2 and the second equivalent of pyridine. The resulting mixture was stirred at 0°C for 1 h. After this time the reaction was quenched with 5 ml 6 N HCl. The layers were separated, the aqueous layer was saturated with NaCl and then extracted with EtOAc (3x150 ml). The combined extracts were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography on silica gel (EtOAc/hexane 1:5) to give (1.03 g, 2.0 mmol) 61% of compound **1** as a yellow oil: $[\alpha]_D^{20}$ = +9.6° (c = 1.3 in $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ = 17.75 (s, br., 1H; CH), 7.22 (d, ^{3}J(H,H) = 8 Hz, 4H; CH), 6.84 (d, ^{3}J(H,H) = 8 Hz, 4H; CH), 4.48 (d, ^{2}J(H,H) = 11 Hz, 2H; CH_2), 4.39 (d, ^{2}J(H,H) = 11 Hz, 2H; CH_2), 4.20 (q, ^{3}J(H,H) = 7 Hz, 2H; CH_2), 4.12 - 3.92 (m, 2H; CH), 3.76 (s, 6H; CH_3), 3.04 (dd, ^{2}J(H,H) = 15 Hz, ^{3}J(H,H) = 7 Hz, 2H; CH_2), 2.72 (dd, ^{2}J(H,H) = 15 Hz, ^{3}J(H,H) = 5 Hz, 2H; CH_2), 1.28 (t, ^{3}J(H,H) = 7 Hz, 3H; CH_3), 1.23 (d, ^{3}J(H,H) = 6 Hz, 6H; CH_3); IR ($CHCl_3$): ν = 1744 cm^{-1} (C=O), 1708 cm^{-1} (C=O); MS (20°C): *m/z* (%): 500 (1.5) [M$^+$], 499 (3.0) [M$^+$-1], 137 (100) [$C_8H_9O_2^+$]; High-res. MS ($C_{28}H_{35}O_8$ [M$^+$-1]): calcd 499.233194; found 499.235474.

(3S)-3-[(p-Methoxybenzyl)-oxy]-butan-1-ol (6): (3S)-Ethyl-3-hydroxybutanoate (21 g, 0.16 mol) and 3.9 g (17 mmol) D(+)-CSA were dissolved in 180 ml CH_2Cl_2. A solution of 86.0 g (0.32 mol) MPM trichloroacetimidate in 30 ml CH_2Cl_2 was added over a period of 10 min. The reaction was stirred for 23 h at room temperature. The precipitated trichloroacetamide was filtered off and washed with CH_2Cl_2. The filtrate was washed with aqueous $NaHCO_3$ and the aqueous layer was back extracted with ether (3x150 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. 56.6 g of the crude product were dissolved in 70 ml ether. This solution was added dropwise to a suspension of 4.02 g (0.106 mol) LAH in 230 ml ether. The mixture was quenched with aqueous $NaHCO_3$ at 0°C after 4 h. The solution was allowed to warm to room temperature, the layers were separated and the aqueous layer was extracted with ether (3x150 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc/hexanes, 1:4) gave the desired alcohol **6** (18.8 g, 90 mmol) in 85% yield as a yellow oil: $[\alpha]_D^{20}$ = +46.3° (c = 1.3 in $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ = 7.25 (d, ^{3}J(H,H) = 8 Hz, 2H; CH), 6.87 (d, ^{3}J(H,H) = 8 Hz, 2H; CH), 4.56 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2), 4.36 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2), 3.78 (s, 3H; CH_3), 3.80 -3.70 (m, 3H; CH, CH_2), 2.86 (s, br., 1H; OH), 1.80 -1.68 (m, 2H; CH_2), 1.23 (d, ^{3}J(H,H) = 6 Hz, 3H; CH_3); IR ($CHCl_3$): ν = 3518 cm^{-1} (OH); MS (20°C): *m/z* (%): 210 (3.8) [M$^+$], 121 (100) [$C_8H_9O^+$]; High-res. MS ($C_{12}H_{18}O_3$): calcd 210.125595; found 210.124587.

(3S)-3-[(p-Methoxybenzyl)-oxy]-butanal (7): To a solution of 9.4 ml (106 mmol) oxalyl chloride in 120 ml CH_2Cl_2 was added 16.3 ml (229 mmol) Me_2SO at -65°C. The reaction mixture was stirred for 15 min

and a solution of 18.5 g (88 mmol) **6** in 30 ml CH_2Cl_2 was added at -65°C. The reaction mixture was stirred for 30 min. Triethylamine (61.3 ml, 440 mmol) was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water was added and the layers were separated. The aqueous layer was extracted with ether (3x150), the organic layers were combined, dried ($MgSO_4$) and concentrated. Flash chromatography (EtOAc/hexanes 1:5) gave the expected aldehyde **7** (8.6 g, 41 mmol) in 47% yield: $[\alpha]_D^{20}$ = +32.0° (c = 1.3 in $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ = 9.75 (t, ^{3}J(H,H) = 2 Hz, 1H; CHO), 7.24 (d, ^{3}J(H,H) = 8 Hz, 2H; CH), 6.87 (d, ^{3}J(H,H) = 8 Hz, 2H; CH), 4.54 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2), 4.39 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2), 4.12 - 3.98 (m, 1H; CH), 3.75 (s, 3H; CH_3), 2.67 (ddd, ^{2}J(H,H) = 16 Hz, ^{3}J(H,H) = 7 Hz, 2 Hz, 1H; CH_2), 2.48 (ddd, ^{2}J(H,H) = 16 Hz, ^{3}J(H,H) = 5 Hz, 2 Hz, 1H; CH_2), 1.28 (d, ^{3}J(H,H) = 6 Hz, 3H; CH_3); IR ($CHCl_3$): ν = 1724 cm^{-1} (C=O); MS (20°C): *m/z* (%): 208 (2.7) [M^+], 137 (100) [$C_8H_9O_2^+$]; High-res. MS ($C_{12}H_{16}O_3$): calcd 208.109945; found 208.110687.

(5S)-Ethyl-3-oxo-5-[(p-methoxybenzyl)oxy]-hexanoate (8): To a suspension of 3.8 g (20 mmol) $SnCl_2$ in 120 ml CH_2Cl_2 was added 12.8 ml (124 mmol) ethyl diazoacetate under vigorous stirring at room temperature. A solution of (3S)-3-[(p-methoxybenzyl)oxy]-butanal (**7**) (8.6 g, 41 mmol) in 20 ml CH_2Cl_2 was prepared. When nitrogen evolution began the remaining solution of aldehyde **7** was added dropwise. After nitrogen evolution had stopped the reaction was transferred to a separatoring funnel containing saturated brine and the layers were separated. The aqueous layer was extracted with ether (3x150 ml), the organic layers were combined, dried over $MgSO_4$ and filtered. After evaporation of the solvent, the crude product was purified by chromatography on silica gel (EtOAc/hexanes 1:5) to give 64% (7.8 g, 26.5 mmol) of compound **8** as a yellow oil: $[\alpha]_D^{20}$ = +24.9° (c = 1.3 in $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ = 7.24 (d, ^{3}J(H,H) = 8 Hz, 2H; CH), 6.86 (d, ^{3}J(H,H) = 8 Hz, 2H; CH), 4.50 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2), 4.37 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2), 4.18 (q, ^{3}J(H,H) = 7 Hz, 2H; CH_2), 4.09 - 3.92 (m, 1H; CH), 3.79 (s, 3H; CH_3), 3.46 (s, 2H; CH_2), 2.85 (dd, ^{2}J(H,H) = 16 Hz, ^{3}J(H,H) = 8 Hz, 1H; CH_2), 2.58 (dd, ^{2}J(H,H) = 16 Hz, ^{3}J(H,H) = 5 Hz, 1H; CH_2), 1.27 (t, ^{3}J(H,H) = 7 Hz, 3H; CH_3), 1.23 (d, ^{3}J(H,H) = 6 Hz, 3H; CH_3); IR ($CHCl_3$): ν = 1740 cm^{-1} (C=O), 1716 cm^{-1} (C=O); MS (20°C): *m/z* (%): 294 (0.7) [M^+], 121 (100) [$C_8H_9O^+$]; High-res. MS ($C_{16}H_{22}O_5$): calcd 294.146724; found 294.146576.

(3S)-3-[(p-Methoxybenzyl)-oxy]-butanoic Acid (9): 28.3 g of compound **5** was dissolved in 84 ml of MeOH/H_2O (3:1). The solution was cooled to 0°C and 12.0 g (0.16 mol) $LiOH{\cdot}H_2O$ (56% LiOH) was added. The solution was stirred for 3 h at room temperature. The reaction was concentrated under water aspirator and acidified with 6 N HCl to pH 1. The aqueous layer was saturated with NaCl and then extracted with EtOAc (3x150 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc/hexanes 1:3) gave acid **9** (10.4 g, 46 mmol) in 88% yield: $[\alpha]_D^{20}$ = +28.0° (c = 1.3 in $CHCl_3$), ^{1}H-NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ = 11.15 (s, br., 1H; CO_2H); 7.25 (d, ^{3}J(H,H) = 8 Hz, 2H; CH), 6.86 (d, ^{3}J(H,H) = 8 Hz, 2H; CH), 4.53 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2), 4.44 (d, ^{2}J(H,H) = 11 Hz, 1H;

CH_2), 4.06 - 3.92 (m, 1H; CH), 3.78 (s, 3H; CH_3), 2.67 (dd, $^2J(H,H)$ = 15 Hz, $^3J(H,H)$ = 7 Hz, 1H; CH_2), 2.46 (dd, $^2J(H,H)$ = 15 Hz, $^3J(H,H)$ = 6 Hz, 1H; CH_2), 1.26 (d, $^3J(H,H)$ = 6 Hz, 3H; CH_3); IR ($CHCl_3$): ν = 1713 cm^{-1} (C=O); MS (20°C): *m/z* (%): 224 (5.3) [M^+], 137 (100) [$C_8H_9O_2^+$]; High-res. MS ($C_{12}H_{16}O_4$): calcd 224.104859; found 224.104935.

(3S)-3-[(p-Methoxybenzyl)-oxy]-butanoic Acid Chloride (10): To a solution of 1.3 g (5.78 mmol) acid **9** in 5.7 ml cyclohexane was added dropwise 0.63 ml (8.67 mmol) of $SOCl_2$. The reaction mixture was heated to 60°C for 1 h. After the solvent and excess $SOCl_2$ were evaporated off, the crude product was used without further purification: IR ($CHCl_3$): ν = 1796 cm^{-1} (COCl).

(2S,8S)-4,6-Oxo-5-carboxyethyl-2,8-hydroxynonane (11): A solution of 1.8 g (3.6 mmol) of **1** in 54 ml CH_2Cl_2 was stirred with 2.9 ml of water, and 2.0 g (8.64 mmol) of 2,3-dichloro-5,6-dicyanoquinone was added. After being stirred for 1 h at room temperature, the mixture was quenched with aqueous $NaHCO_3$, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3x150 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel with EtOAc/hexane 1:1 to yield 59% (555 mg, 2.1 mmol) **11**: $[\alpha]_D^{20}$ = -77.56° (c = 1.6 in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ = 4.72 - 4.53 (m, 1H; CH), 4.30 (q, $^3J(H,H)$ = 7 Hz, 2H; CH_2), 4.22 - 4.08 (m, 1H; CH), 2.79 - 2.46 (m, 4H; CH_2), 1.50 (d, $^3J(H,H)$ = 6 Hz, 3H; CH_3), 1.34 (t, $^3J(H,H)$ = 7 Hz, 3H; CH_3), 1.29 (d, $^3J(H,H)$ = 6 Hz, 3H; CH_3); IR ($CHCl_3$): ν = 3432 cm^{-1} (OH), 1728 cm^{-1} (C=O), 1680 cm^{-1} (C=O); MS (FAB): *m/z* (%): 243 (96) [M^+-17], 197 (100) [$C_{10}H_{16}O_4^+$].

(2R,6S,2'S)-Tetrahydro-2-propan-2'ol-3-carboxyethyl-6-methyl-4H-pyran-4-one (12): To a solution of 437 mg (1.68 mmol) of diol **11** in 60 ml THF/MeOH (5:1) was added a solution of 0.5 ml (4.37 mmol) $TiCl_4$ in 4.0 ml CH_2Cl_2 at -78°C. After 45 min, 5.75 ml of 2M $LiBH_4$ in THF was added dropwise. After being stirred for 2 h at -78°C the reaction was quenched with aqueous $NaHCO_3$. The layers were separated, the aqueous layer saturated with NaCl and extracted with EtOAc (3x150 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Chromatography of the crude product with silica gel using hexanes/EtOAc 3:1 as eluent provided 77% (309 mg, 1.3 mmol) **12** as a colorless oil: $[\alpha]_D^{20}$ = +45.2° (c = 1.3 in $CHCl_3$); ^1H-NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ = 4.23 (q, $^3J(H,H)$ = 7 Hz, 2H; CH_2), 4.35 - 4.06 (m, 2H; CH), 3.97 - 3.79 (m, 1H; CH), 3.31 (d, $^3J(H,H)$ = 11 Hz, 1H; CH), 2.50 (dd, $^2J(H,H)$ = 15 Hz, $^3J(H,H)$ = 3 Hz, 1H; CH_2), 2.29 (dd, $^2J(H,H)$ = 15 Hz, $^3J(H,H)$ = 11 Hz, 1H; CH_2), 1.85 - 1.58 (m, 2H; CH_2), 1.35 (d, $^3J(H,H)$ = 6 Hz, 3H; CH_3), 1.29 (t, $^3J(H,H)$ = 7 Hz, 3H; CH_3), 1.23 (d, $^3J(H,H)$ = 6 Hz, 3H; CH_3); IR ($CHCl_3$): ν = 3532 cm^{-1} (OH), 1740 cm^{-1} (C=O), 1716 cm^{-1} (C=O); MS (120°C): *m/z* (%): 243 (1.1) [M^+-1], 185 (49.9) [$C_9H_{13}O_4^+$], 139 (100) [$C_7H_7O_3^+$]; High-res. MS ($C_{12}H_{19}O_5$ [M^+-1]): calcd 243.123249; found 243.123016.

(2S,7S,8'R)-4-Hydroxy-2,7-dimethyl-3,7,8,8'-tetrahydro-2H-pyrano-[4,3-b]pyran-5-one (13): A solution of 280 mg (1.15 mmol) of **12** in 25 ml CH_2Cl_2 was stirred at room temperature and 245µl (3.21 mmol) of CF_3CO_2H was added. After being stirred for 22 h at room temperature the reaction was quenched with aqueous $NaHCO_3$, the layers separated and the organic layer extracted with EtOAc (3x150 ml). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was evaporated off. The crude product was purified on silica gel (EtOAc/hexane 1:5) to give 56% (127 mg, 0.64 mmol) of **13** as colorless crystals: M.p. 86°C; $[\alpha]_D^{20}$ = +19.6° (c = 1.3 in $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ = 12.69 (s, 1H; OH), 4.55 - 4.32 (m, 2H; CH), 3.97 - 3.78 (m, 1H; CH), 2.47 - 2.29 (m, 2H; CH_2), 2.23 (ddd, ^{2}J(H,H) = 12 Hz, ^{3}J(H,H) = 5 Hz, 2 Hz, 1H; CH_2), 1.65 (q, ^{2,3}J(H,H) = 12 Hz, 1H; CH), 1.43 (d, ^{3}J(H,H) = 6 Hz, 3H; CH_3), 1.32 (d, ^{3}J(H,H) = 6 Hz, 3H; CH_3); IR ($CHCl_3$): ν = 1656 cm^{-1} (C=O), 1616 cm^{-1} (=OH); MS (20°C): *m/z* (%): 198 (25.3) [M$^+$]; Anal. Calcd for $C_{10}H_{14}O_4$ (198.2): C 60.60, H 7.07. Found: C 60.71, H 7.07.

(2S,4R,7S,4'R,8'R)-4-Hydroxy-2,7-dimethyl-hexahydro-pyrano[4,3-b]pyran-5-one (14): A solution of 110 mg (0.55 mmol) of **13** in 12 ml EtOH was hydrogenated with 5 mol% Pd/C as catalyst at 40°C and a pressure of 3.0 bar H_2. After 50 h the solution was filtered through a plug of Celite. The solvent was evaporated and the residue was chromatographed with EtOAc to yield 81% (88 mg, 0.44 mmol) of **14** as colorless crystals: M.p. 98°C; $[\alpha]_D^{20}$ = +12.0° (c = 0.25 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C, TMS): δ = 4.38 - 4.29 (m, 1H; CH), 3.94 (dt, ^{3}J(H,H) = 9.10 Hz, 2.95 Hz, 1H; CH), 3.89 (d, ^{3}J(H,H) = 11.93 Hz, 1H; OH), 3.86 - 3.77 (m, 1H; CH), 3.41 (ddq, ^{3}J(H,H) = 12.47 Hz, 6.21 Hz, 2.15 Hz, 1H; CH), 2.77 (t, ^{3}J(H,H) = 4.07 Hz, 1H; CH), 2.41 (ddd, ^{2}J(H,H) = 13.09 Hz, ^{3}J(H,H) = 9.06 Hz, 4.03 Hz, 1H; CH_2), 1.93 - 1.85 (m, 1H; CH_2), 1.74 - 1.60 (m, 2H; CH_2), 1.41 (d, ^{3}J(H,H) = 6.21 Hz, 3H; CH_3), 1.20 (d, ^{3}J(H,H) = 6.21 Hz, 3H, CH_3); IR ($CHCl_3$): ν = 3520 cm^{-1} (OH), 1728 cm^{-1} (C=O); MS (20°C): *m/z* (%): 200 (2.5) [M$^+$]; Anal. Calcd for $C_{10}H_{16}O_4$ (200.2): calcd C 60.00, H 8.00. Found: C 59.99, H 7.88.

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