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Rubrenolide, total synthesis and revision of its reported stereochemical structure

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Abstract—In this paper the synthesis of the natural product rubrenolide is presented. Due to an error in the original proposed stereochemical structure of rubrenolide, the synthesis was not straightforward. Application of the photo-induced rearrangement of an appropriate epoxy diazomethyl ketone gave access to the precursor lactone with an ee of 91%. Coupling of this lactone with (4*S*)-2,2-dimethyl-[1,3]-dioxolane-4-carbaldehyde gave, after some additional steps, the final product that was identical with an authentic sample of the natural product.

1. Introduction

Rubrenolide **1** is a natural product which has been isolated from trunk wood of the Amazonian tree *Nectandra rubra* of the Lauraceae family. Its chemical constitution was first published in 1971.[1] Actually, rubrenolide **1** was isolated as a mixture with an analog—rubrynolide **2**, which only differs in the terminal unsaturated bond in the aliphatic side chain (Fig. 1). The biosynthesis of these compounds was also described.[2] In 1977 the full structure, including assignment of the configuration at the chiral centers, was reported.[3] The assignment of the configuration of rubrenolide was made according to the denotation of the structure in Figure 1 and it was named (2*S*,4*R*)-2-[(2′*S*)-2′,3′-dihydroxypropyl]-4-(dec-9i″-enyl)-γ-lactone.† According to this structure the substituents at C_2 and C_4 have a *cis* relationship. It is important to note here that in assigning the *R*/*S* descriptors great care should be exercised by the correct use of the priority rules,[4] which often are not straightforward. In Figure 2 the priority

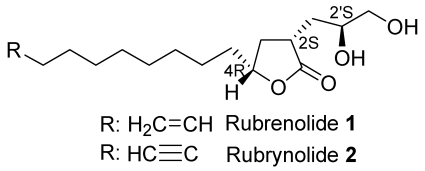

Figure 1.

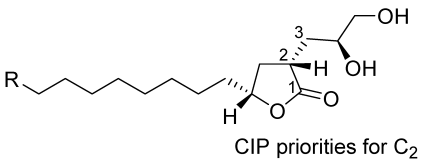

Figure 2.

of the groups attached to the chiral center C_2 is depicted for the sake of clarity.

In the paper by Franca et al.[3] concerning the absolute configuration of rubrenolide and rubrynolide the following phrase is puzzling: '*The complete assignment of all proton resonances and coupling constants associated with the γ-lactone showed rubrenolide to possess the 2,4-trans configuration. Comparison with analogous data given by some model cis (**7**) and trans (**8**) 2,4-disubstituted γ-butyrolactones, specially synthesized for this purpose, yielded unequivocal proof of this fact*'.

Because of the very detailed NMR studies that were carried out on rubrenolide and the model compounds mentioned,[5] it must be assumed that an interchange of two figures (denoted there as 7 and 8, see quote) has taken place in the final paper,[3] leading to the incorrect statement that the substituents at C_2 and C_4 are positioned *trans*.

An approach to the synthesis of rubrynolide **2**, reported by Taylor et al.[6] in 1991, was regrettably not noticed by us at that time. This synthesis was based on a reaction of an epoxide with an aluminum enolate, which leads to lactone **3** as a *trans*–*cis* mixture in a ratio of 85:15 (Scheme 1). Dihydroxylation of the olefinic bond with OsO_4 resulted in a mixture of four racemic components, namely *cis R* alcohol

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† Throughout the text the original nomenclature will be used, describing rubrenolide as a γ-lactone. In Section 5 the names generated by the Beilstein Autonom version 2.1 program will be used describing a γ-lactone as dihydrofuran-2-one.

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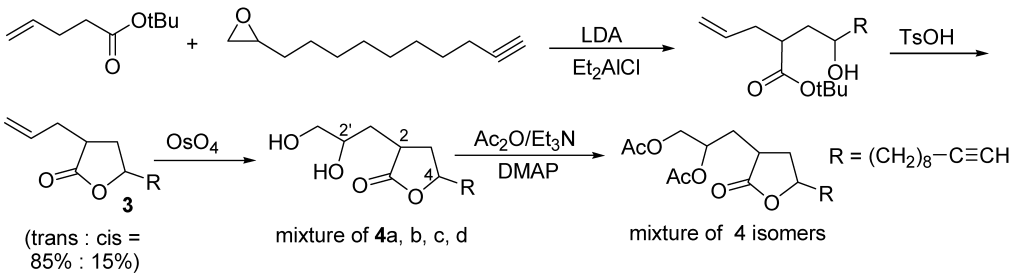


Scheme 1.

4a, *cis S*-alcohol **4b**, *trans R*-alcohol **4c**, and *trans S*-alcohol **4d**. Their configurations relative to the 4*R* configuration are 2*S*,4*R*,2′*R* for **4a**, 2*S*,4*R*,2′S for **4b**, 2*R*,4*R*,2′*R* for **4c** and 2*R*,4*R*,2′*S* for **4d**. Only one of the minor products was, according to the NMR analysis of the mixture, identical with rubrynolide, which implies either structure **4a** or **4b**. As the diols could not be separated, they were converted into their diacetates, which could be separated by HPLC. One product was identical with the diacetate of rubrynolide. Taylor et al. assumed that the originally assigned *R* configuration of C_4 was correct, that C_2' has the *S* configuration, and that the diacetate derived from **4b** was identical to rubrynolide diacetate, which then should have the 2*S*,4*R*,2′*S* configuration. This is exactly the same configuration as was reported by Franca et al. Notwithstanding, Taylor et al. entitled their paper as 'Synthesis of (±)-rubrynolide and a revision of its reported stereochemistry'.

It seems that Taylor et al. refer to the phrase of Franca, which is cited above in italics, stating that rubrenolide and rubrynolide have the 2,4-*trans* relationship (which is incorrect vide supra). The total synthesis of natural rubrenolide as carried out by the Nijmegen group,[7] unambiguously showed that the correct absolute configuration of this product is 2*S*,4*R*,2′*R*.

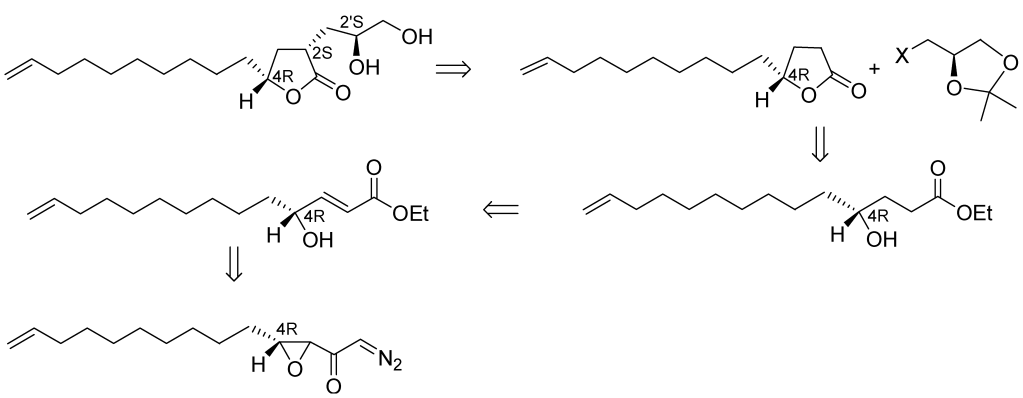
The total synthesis of the naturally occurring functionalized γ-lactone rubrenolide **1** offers an opportunity to test the applicability of the synthetic methodology based on epoxy diazomethyl ketones.[8] The key reaction in this methodology for the synthesis of γ-lactones is the photo-induced rearrangement of epoxy diazomethyl ketones to epoxy ketene followed by a domino reaction with an alcohol to give γ-hydroxy-α,β unsaturated esters.[9] The introduction of the side chain in rubrenolide in a stereocontrolled manner constitutes an extra challenge. The retrosynthesis of rubrenolide with the proposed (2*S*,4*R*,2′*S*)-configuration is outlined in Scheme 2. The stereochemistry at C4 is derived from the epoxy diazomethyl ketone and can be introduced as required by choosing the appropriate chiral inductor during the Sharpless epoxidation that is used in the synthesis of the epoxy unit. The side chain can possibly be introduced by an alkylation reaction, which may give rise to *cis*/*trans* mixtures that hopefully can be separated.

2. Results

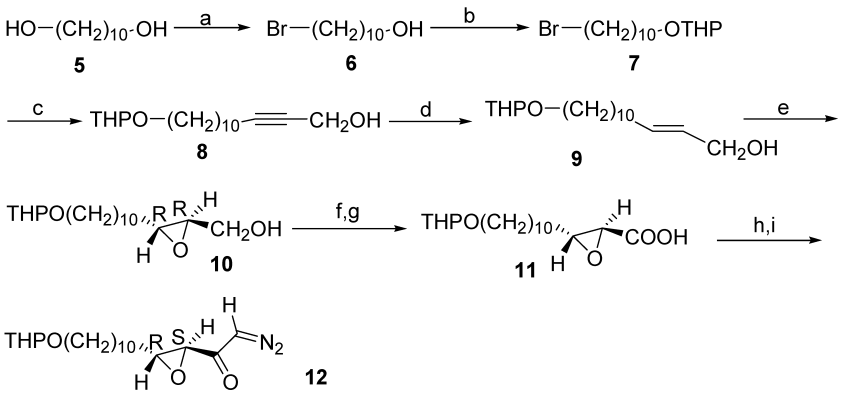
2.1. Synthesis of rubrenolide with the proposed (2*S*,4*R*,2′*S*)-configuration

The synthesis of the required epoxy diazomethyl ketone **12** started with decane-1,10-diol **5** which was treated with hydrobromic acid to give the bromo alcohol **6** (Scheme 3). After protection of the alcohol as a THP ether (compound **7**) a chain elongation with the dianion of propargylic alcohol was carried out. The alkynol **8** was reduced with $LiAlH_4$ to give the *trans* allylic alcohol **9** with high efficiency. In the next step the required chirality had to be installed by choosing the right chiral inductor in the Sharpless epoxidation.[10] In order to obtain the 4*R* configuration in the natural product **1** D-(−) diethyl tartrate was needed for this purpose. The (2*R*,3*R*)-epoxy alcohol **10** thus obtained needed to be oxidized to the corresponding carboxylic acid. The one-step oxidation procedure with RuO_4 was not possible in this case due to the vulnerability of the THP protecting group.

The Swern oxidation to the aldehyde, followed by further oxidation with sodium chlorite[11] to the carboxylic acid was a perfect alternative. The thus obtained carboxylic acid **11**



Scheme 2.



Scheme 3. (a) HBr (48%), pet. ether 80–100 °C (73%); (b) DHP, TsOH (94%); (c) $LiNH_2$ 6 equiv., propyn-2-ol-1, 3 equiv., (99%); (d) $LiAlH_4$, 2 equiv., (quant.); (e) D-(−)-DET, Ti(*i*OPr)$_4$, *t*-BuOOH (69%); (f) Swern oxid.(quant.); (g) $NaClO_2$ (quant.); (h) *i*-butyl chloroformate, Et_3N; (i) CH_2N_2 (68%, calcd on epoxy alcohol **10**).

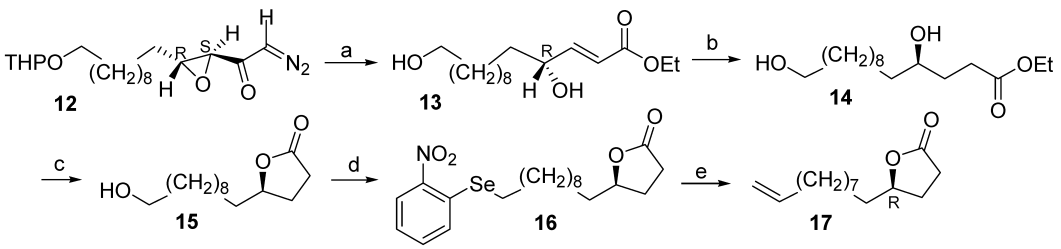
was converted into the epoxy diazomethyl ketone **12** by reaction with iso-butyl chloroformate and triethylamine to give the mixed anhydride and subsequent treatment with ethereal diazomethane. The diazo ketone **12** was purified by chromatography and obtained in an acceptable overall yield (Scheme 3).

The next step in the sequence to the γ-lactone **17** is the photo-induced rearrangement of epoxy diazomethyl ketone **12** in ethanol as the solvent. This reaction was monitored by IR. Unexpectedly, the THP protecting group was lost completely during this reaction (Scheme 4). The product obtained after irradiation, i.e. the γ-hydroxy-α,β-unsaturated ester **13**, preferably is used for further reactions without purification.[12] Thus, product **13** was subjected to reduction with P2–Ni[13] as the catalyst to give the dihydroxy carboxylic ester **14**. Subsequent lactonization to γ-lactone **15** was accomplished by treatment with TsOH in benzene at reflux temperature.

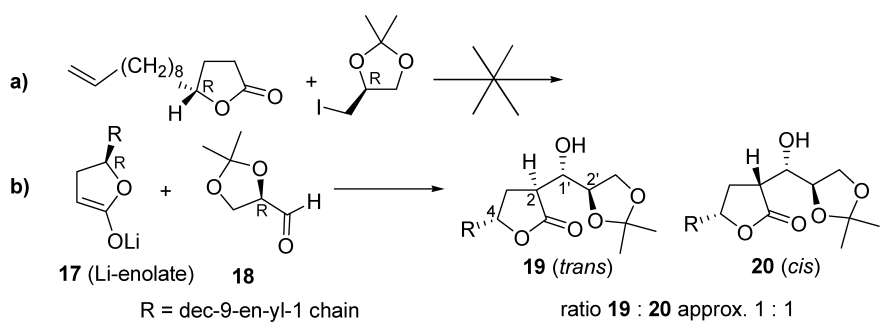
For the next step, the introduction of the terminal olefinic bond, *o*-nitrophenylselenyl cyanide was used as the reagent.[14] Although this ingredient is not very pleasant, the formation of selenide **16** and the subsequent elimination reaction to give lactone **17** took place smoothly (Scheme 4). Product **17** was slightly yellow due to impurities arising from the nitrophenylselenyl reagent.

The planned alkylation step was attempted with (4*R*)-4-iodomethyl-2,2-dimethyl-[1,3]-dioxolane using the Li-enolate of lactone **17** (Scheme 5(a)). Despite the use of a range of reaction conditions, the desired coupling could not be realized. Apparently, this alkylating agent is very reluctant to undergo an S_N2 reaction with an enolate anion. An alternative candidate electrophile for the introduction of the side chain is (4*R*)-2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde **18**.[15]

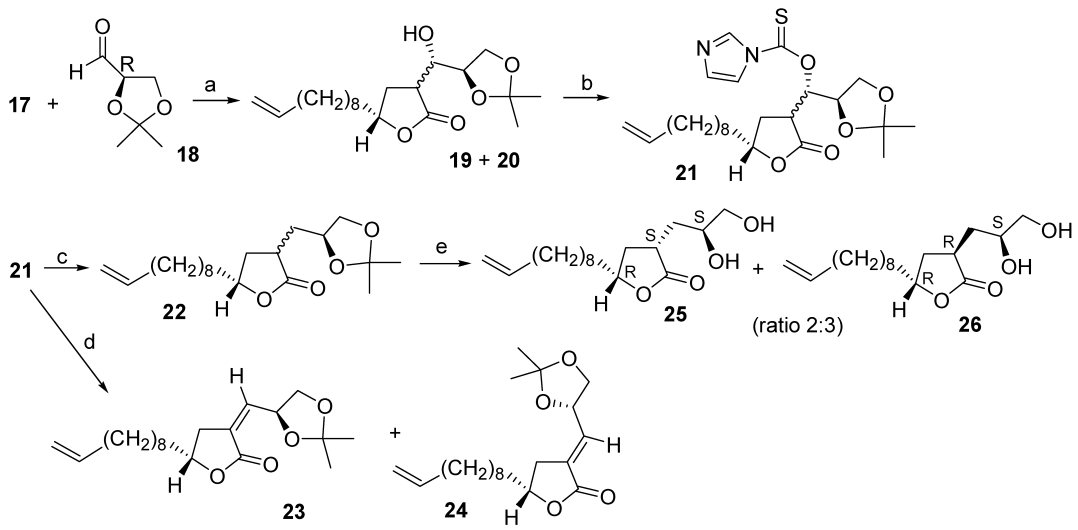
The enolate of **17** reacted smoothly with aldehyde **18** to give



Scheme 4. (a) *hν*, 300 nm, EtOH; (b) $Ni(OAc)_2$, $NaBH_4$ (57% calcd on **12**); (c) TsOH, benzene (quant.); (d) *o*-NO_2PhSeCN, Bu_3P (93%); (e) H_2O_2, Na_2CO_3 (68%).



Scheme 5.



Scheme 6. (a) LDA, THF, HMPA, (80%); (b) thiocarbonyl diimidazole (64%); (c) Bu_3SnH, toluene, gentle warming, (70%); (d) Bu_3SnH, toluene, reflux, (64%); (e) TsOH, MeOH, (61%).

a mixture of two major products (ratio 1:1) as was deduced from a GLC analysis. Tentatively, structures **19** and **20** were assigned to these condensation products (Scheme 5, line b). If the assignment of the Aldol products **19** and **20** is correct, then it will be possible to prepare the rubrenolide type product with the *cis* as well as the *trans* configuration. For the transformation of the Aldol products into the final products the alcohol function at C_1' has to be removed. An attractive approach would be the conversion into a thio-imidazolide **21** and a subsequent reduction with tributyltin hydride[16] (Scheme 6).

The formation of the thio-imidazolide **21** was accomplished in THF at room temperature for 6 h, in a yield of 64%. Some starting material (21%) was recovered and some by-products, mainly a mixture of **23** and **24** were isolated. Repeating the same reaction at reflux temperature for 3 h gave product **21** (55%), starting material (20%) and a mixture of **23**+**24** (22%).

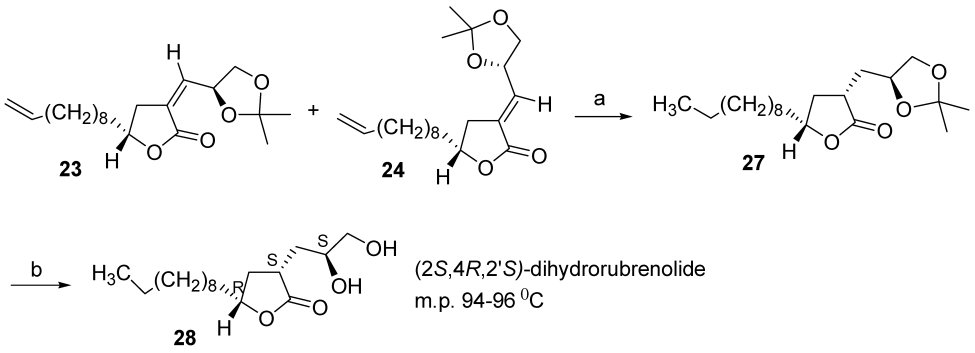
For the reductive removal of the thio-imidazolide group in **21** the method described by Rasmussen et al.[16] was followed, namely reaction with tributyltin hydride in toluene at reflux temperature. A mixture of the unsaturated compounds **23** and **24** was obtained in 64% yield. These geometrical isomers could be separated by chromatography and the structures could be assigned on the basis of the ^1H NMR spectra.[17] Unexpectedly, the product **22** had not been obtained under these conditions. However, repeating the reaction at lower temperature, i.e. after addition of freshly prepared tributyltin hydride, the reaction mixture was gently heated for 30 min, resulted in the desired product **22** in 70% yield and almost no unsaturated product was obtained. According to GLC this product consisted of two isomers (as expected), however, chromatographic separation on silica gel was not possible. Hydrolysis of the product **22** by treatment with TsOH in methanol gave the deprotected product, which according to GLC and TLC, was not a mixture of isomers. However, the presence of the expected two isomers was demonstrated by ^1H NMR spectroscopy (400 MHz). The products were identified as the *cis* and *trans* compounds **25** and **26** (product ratio 2:3). **'Surprisingly, neither of these two products was the expected rubrenolide'.**‡

This conclusion was further substantiated as follows. Hydrogenation of the mixture of the unsaturated compounds **23** and **24** gave a single product as was shown by GLC analysis. Indeed, catalytic hydrogenation should produce the *cis*-disubstituted lactone **27** (Scheme 7). Predictably, the terminal olefin is hydrogenated as well. This saturated compound **27** (mp 38–41 °C) should then be identical to the dihydrorubrenolide derivative obtained by Franca et al.[3] by reaction of dihydrorubrenolide with acetone.

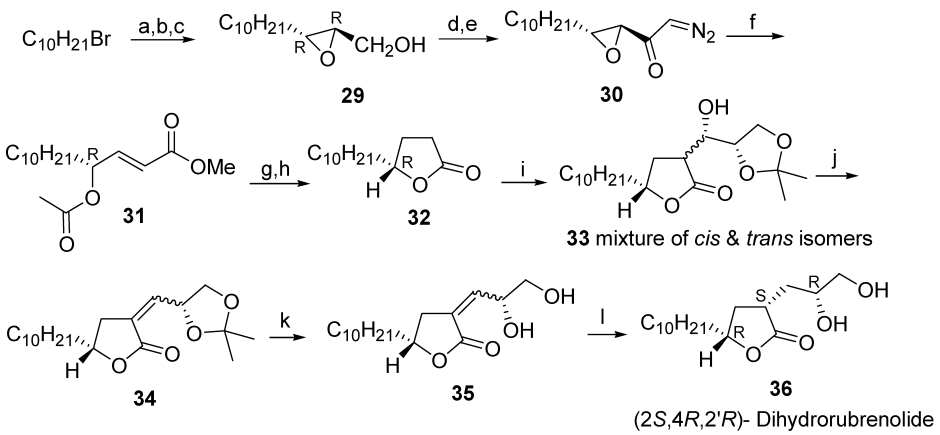
The spectral data however were not in agreement with those reported[3] and the melting points were different as well (lit.[3] mp 47–48 °C). When the acetonide unit was hydrolyzed, product **28** with mp 94–96 °C was obtained, which, according to its mp and NMR spectrum§ clearly was not dihydrorubrenolide as described by Franca et al.[3] (mp dihydrorubrenolide: 106–107 °C). Thus the (2*S*,4*R*,2′*S*) configuration is not in agreement with the true structure of rubrenolide. The unambiguous conclusion is that the proposed absolute configuration of 2*S*,4*R*,2′*S* by Franca et al.[3] for dihydrorubrenolide and rubrenolide is not correct. In addition, the results also indicate that the 2*R*,4*R*,2′*S* configuration, as in *trans* disubstituted lactone **26**, is not dihydrorubrenolide either.

‡ Compound **25** (*cis* substituted lactone) is an epimer of rubrenolide at the C2′ position. The *trans* disubstituted lactone **26** shows ^1H NMR absorptions identical with one of the *trans* dihydroxy-propyl lactones described in Ref. 6. The compound is denoted as *trans*-alcohol **4d** in Scheme 1.

§ The late Professor Ollis, kindly provided us with a free sample of the natural product consisting of a mixture of rubrenolide and rubrynolide. The two products could be separated as reported.[3] Rubrynolide was hydrogenated to give dihydrorubrenolide (see Section 5).



Scheme 7. (a) H2, Pd/C, quant.; (b) TsOH, MeOH, quant.



Scheme 8. (a) Propyn-2-ol-1, 3 equiv., $LiNH_2$ 6 equiv., (90%); (b) $LiAlH_4$, 2 equiv., (85%); (c) (D)-(−)-DET, $Ti(OiPr)_4$, TBHP, (77%); (d) $RuCl_3{\cdot}3H_2O$, $NaIO_4$; (e) *i*-BuO(C═O)Cl, Et_3N, CH_2N_2, (47%); (f) *hν*, 300 nm, MeOH; Ac_2O, pyridine, (50%); (g) $PdCl_2$, $NaBH_4$, H_2, (76%); (h) KOH/EtOH, reflux, 15 min, TsOH, benzene, reflux, quant.; (i) LDA, DMPU, (4S)-2,2-dimethyl-[1,3]-dioxolane-4-carbaldehyde **38**, (63%); (j) MsCl, pyridine, DBU, (96%); (k) TsOH, MeOH, (77%); (l) Pd/C, H_2, EtOH, (84%).

2.2. Synthesis of rubrenolide with the correct (2*S*,4*R*,2′*R*) configuration

As mentioned above it seemed reasonable that the C_2' configuration is opposite to the original assignment. Therefore, the synthesis of dihydrorubrenolide using (4*S*)-2,2-dimethyl-[1,3]-dioxolane-4-carbaldehyde **38** (the antipode of aldehyde **18**) to install the *R*-chirality at C_2', was undertaken.

This synthesis of dihydrorubrenolide (Scheme 8) follows the general sequence for the preparation of lactones. Reaction of decyl bromide with the di-anion of propargyl alcohol, reduction to the *trans*-allylic alcohol, Sharpless epoxidation with D-(−) DET as chiral inductor, RuO_4 oxidation to the glycidic acid, activation of the acid followed by treatment with diazomethane, gave the epoxy diazomethyl ketone **30** in good yield. Irradiation in MeOH and subsequent acetylation gave **31**, reduction of the double bond and ring closure resulted in the desired lactone **32**. The synthesis of this lactone was reported previously as the reduction product of the sex pheromone *cis*-4*R*-4-(1′-decenyl)-γ-lactone[18] of the Japanese beetle.¶ The enantiopurity of the lactone **32** was determined via ^1H NMR of the acetate **31** (by the use of chiral shift reagent) and appeared to be 91%.[19]

The introduction of the side chain was performed by a condensation of the lactone **32** with (4*S*)-2,2-dimethyl-[1,3]-dioxolane-4-carbaldehyde[20] **38**. The thus obtained *cis*/*trans* mixture of alcohol **33** was treated with mesyl chloride to give the corresponding mesylate, which was subjected to an elimination reaction by treatment with DBU giving alkene **34** as a *cis*/*trans* mixture. Catalytic hydrogenation was best performed after deprotection of the vicinal alcohols. Deprotected diol **35** was then hydrogenated using Pd(C) as the catalyst to produce (2*S*,4*R*,2′*R*)-dihydrorubrenolide **36**, which, gratifyingly, was identical to the dihydrorubrenolide prepared from an authentic sample of rubrenolide. The conclusion can be drawn that the absolute configuration of natural rubrenolide must be 2*S*,4*R*,2′*R*.

The total synthesis of natural rubrenolide, having the terminal olefinic bond, was prepared from epoxy diazomethyl ketone **12** as the key starting material, following the synthetic sequence shown in Scheme 3. The photo-induced rearrangement of **12** could be conducted in this case without the loss of the THP protecting group, thus providing **13**-OTHP, which was reduced with P2-Ni/H_2 to the γ-hydroxy ester which was ring closed to the lactone **37**

¶ Although the configuration at the chiral centre of this natural product was assigned correctly as *R*, the reduction product was also given the *R* configuration, which is violating the CIP rules, because the change in priority has not been implemented.

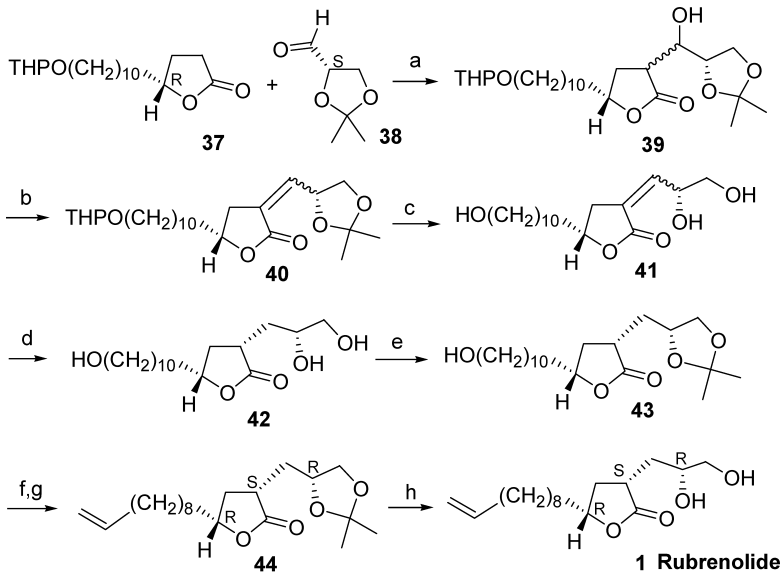
(compare synthesis of lactone **15** shown in Scheme 4). Condensation of lactone **37** with the 4(*S*)-carbaldehyde **38** smoothly led to product **39** (mixture of *cis*/*trans* isomers) (Scheme 9). The *exo* double bond was introduced by elimination of the mesylate using DBU as the base (compare Scheme 8). The thus obtained product **40** (mixture of *cis* and *trans*) was treated with acid to remove both protective groups to give triol **41**, which on catalytic hydrogenation (Pd/C, H_2) afforded the single product **42**, as was evident from its narrow melting range. For the final introduction of the terminal olefinic bond the vic. diol had to be protected as the acetonide **43**. Then the primary hydroxy group was converted into the alkene **44**, following the procedure shown in Scheme 4 using *o*-nitrophenylselanyl cyanide. Finally, removal of the acetonide protecting group gave the target product **1**, whose spectral features and mp were in full agreement with those of the natural product that was kindly provided by (the late) Professor Ollis.

3. Discussion

Having established that rubrenolide does not have the proposed[3] (2*S*,4*R*,2′*S*)-configuration, the question arose what would be the alternative. The original assignment of the configuration at C_4 seemed quite reliable. This was deduced by application of Hudson's lactone rule.[21] In simple terms this rule states that when the lactone is drawn in the Fischer projection (Fig. 3(a)) and the lactone ring lies to the right then the rotation is (+). When the lactone structure is drawn in an alternative way (Fig. 3(b)) then the rule states that if the hydrogen lies below the plane of the lactone ring, the compound will have a (+) rotation. This Hudson lactone rule is supported by numerous examples. It also predicts the rotation and configuration of the simple 4-monosubstituted γ-lactones. When more stereogenic centers are present the situation changes. When the rule is applied to muricatacin (Fig. 3(c)) the predicted optical rotation is not in agreement with the configuration of the chiral center of the lactone.

This problem can be solved by implying the Cotton effect. The contribution of the chiral lactone ring to the optical rotation can be estimated by subtracting the measured rotation of a reference compound without the lactone ring. This, for instance, could be the open form: hydroxy acid or hydroxy ester. The o.r.d. curves of the lactone and a reference compound can be measured and a difference curve can be obtained by subtraction. The sign of the difference curve can now be related to the configuration at the chiral lactone site (a positive sign means that the configuration is *R*). The Cotton effect measures the rotation at the ultraviolet absorption of the lactone function (normally between 225 and 233 nm). The sign of the Cotton effect is in agreement with the sign of the difference curve and thus can be used to determine the contribution of the lactone ring to the optical rotation. Rubrenolide showed a positive Cotton effect at 226 nm (ϕ+1700). This means that rubrenolide has the (*R*)-configuration at C_4.

Accepting this assignment, two possible diastereomers remain, viz. 2*S*,4*R*,2′*R*; and 2*R*,4*R*,2′*R* because the (2*S*,4*R*,2′*S*) and (2*R*,4*R*,2′*S*)-configuration were already excluded. Closer examination of the 400 MHz NMR spectra revealed that the difference between the synthesized product **28** (Scheme 7) and dihydrorubrenolide derived from the natural product[22] is caused by the environment of the hydroxy at C_2'. Franca et al.[3] who reported the complete structure of rubrenolide, determined the configuration at C_2' by applying Horeau's method[23] to the monomethyl ether of the primary alcohol of the natural product. The free secondary alcohol was brought into reaction with α-phenylbutyric anhydride in the presence of pyridine. Hydrolysis of the remaining anhydride gave the acid with a positive rotation. This result then was related to a Fischer projection (Fig. 4), which according to Horeau's method leads to the *S*-configuration at the C_2' chiral center. It is important to note that Horeau and Kagan[24] state in a footnote in their paper of 1964 that when a polar group is close to the secondary alcohol, other rules for the assignment of L and M in the Fischer projection may be necessary.



Scheme 9. (a) LDA, HMPA, THF, −70 °C, 16 h, (26%); (b) MsCl, Et_3N, DBU, (72%); (c) TsOH, MeOH, (70%); (d) Pd/C, H_2, quant.; (e) TsOH, acetone, (73%); (f) *o*-nitro-phenylselanyl cyanide, Bu_3P, (91%); (g) H_2O_2; (h) TsOH, MeOH, (60%).

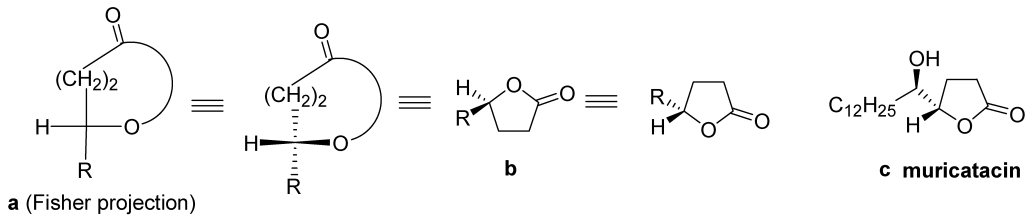


Figure 3.

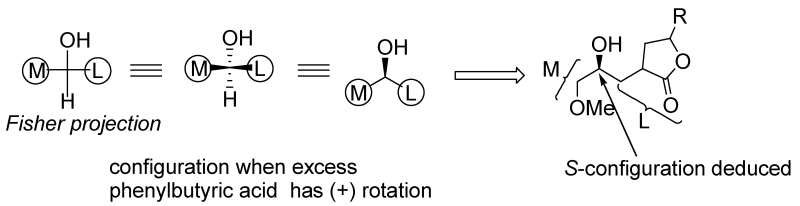


Figure 4.

This special situation is encountered in the case of rubrenolide because of the methoxy group and leads to a deviant priority of M and L, with the ultimate consequence that the assignment of the chirality at C_2' by Franca et al.[3] is not correct.

Concerning Scheme 5 it was assumed that a mixture of *cis* and *trans* substituted lactone products was obtained. A more detailed representation of the possible Aldol condensation products is depicted in Scheme 10. The (*R*)-aldehyde **18** is taken as an example.

It should be noted that the *R* descriptor for the chirality changes to *S* in the final product due to a change in the priority of the substituents flanking this chiral center.

Conclusive information about these structures was obtained by comparison with related condensations reported in the literature and by applying the Felkin–Ahn rule[25] for the reaction of an enolate with a carbonyl compound. The reaction of the Li-enolate of methyl propanoate with carbaldehyde **18** results in the formation of a mixture of *anti*/*syn* and *anti*/*anti* product in a ratio of 3:2 (Scheme 10, line b).[26] Thus this condensation exhibits an exclusive *anti* selectivity with respect to the dioxolane ring. The selectivity with respect to the ester moiety is rather low as is apparent from the *anti*,*syn*/*anti*,*anti* ratio of 3:2. The Felkin–Ahn model for the reaction of aldehyde **18** is shown in Figure 5.[‖] This picture is in agreement with the proposed mechanism described by Jurczak et al.[27] By calculating minimum energy structures of aldehyde **18**, attack of the nucleophile leads to the same result (Fig. 5).[28] Clearly, the *syn* attack is disfavored ruling out structures C and D. It is reasonable to assume that the condensation of the enolate of **17** with aldehyde **18** also proceeds with a high selectivity with respect to the dioxolane ring,[29] implying the preferred formation of the *anti*/*syn* and *anti*/*anti* products shown in Scheme 10, line a. Taking into account that the chirality at C_4 and C_2' is defined by the starting materials, the product mixture A+B is to be expected.

[‖] The representation of the Felkin–Ahn model was misinterpreted in the first draft of this paper as was pointed out by one of the referees.

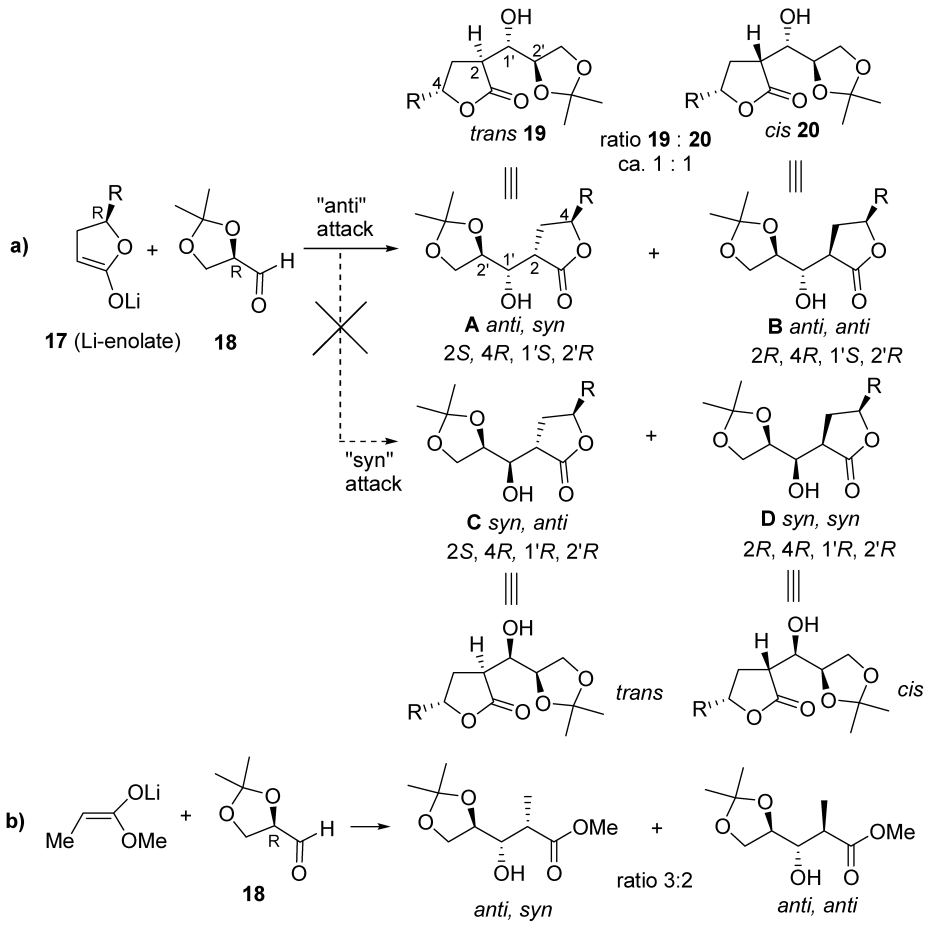
4. Concluding remarks

The absolute configuration of the natural products rubrenolide and rubrynolide has been established by a fully stereoselective total synthesis. The originally assigned (2*S*,4*R*,2′S)-configuration turned out to be incorrect, the configuration at C_2' is opposite. In the original paper of Franca et al.[3] dealing with the absolute stereochemical structure of these natural products, an incorrect and confusing statement concerning the *cis*/*trans* geometry was made. In the synthetic strategy effective use was made of the chemistry of epoxy diazomethyl ketones, in particular the photo-induced rearrangement in an alcoholic solution leading to γ-hydroxy-α,β-unsaturated esters, which conveniently can be converted to γ-lactones with a designed chirality at C_4, when optically active substrates are used.

5. Experimental

5.1. General remarks

The solvents used for synthetic procedures and for chromatography were purified and dried according to conventional methods. Melting points were determined using a Reichert thermopan microscope and are uncorrected. IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer or on a FTIR spectrophotometer of ATI Mattson (Genesis Series). NMR's were measured on different instruments: routinely ^{1}H spectra with a Varian EM-390, or a Bruker AC 100 (100 MHz, FT) instrument. More detailed spectra requiring also ^{13}C data were measured on a Bruker AM-400 (400 MHz, FT) instrument. Optical rotations were measured with a Perkin–Elmer 241 MC automatic polarimeter. Mass spectra were run on a double focusing VG 7070E instrument. Elemental analyses were performed using a Carlo Erba Instruments CHNS–O 1108 element analyzer. GLC's were run using



Scheme 10.

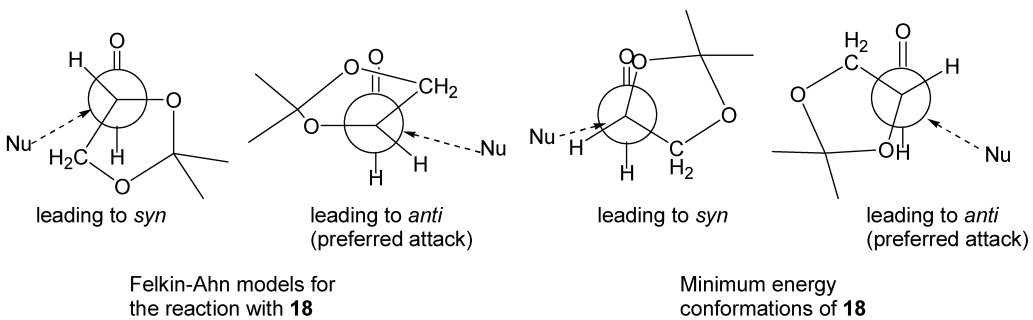


Figure 5.

Hewlett–Packard 5790 or 5890 instruments, equipped with apolar capillary columns. TLC's were performed using glass plates coated with 25 mm silica (Merck 60 F-254). Spots were visualized with a 6.2% H_2SO_4 solution (1 L) containing ammonium molybdate (42 g) and cerium ammonium sulfate (3.6 g), followed by charring. For 'normal' chromatography silica gel 60 (Baker) was used. For flash chromatography Kieselgel 60H (Merck) was applied.

5.1.1. 10-Bromo-decan-1-ol 6.[30] Decane-1,10-diol **5** (47.0 g, 0.27 mol) was mixed with hydrobromic acid (380 mL, 47%) in a Dean–Stark apparatus (1 L size) and the mixture was extracted continuously with petroleum ether (bp 80–100 °C) during 60 h. The organic layer was collected and shaken with solid K_2CO_3. After filtration the filtrate was concentrated in vacuo and the residue was purified by flash chromatography (hexane–diethyl ether 8:1, removal of dibromide, followed by diethyl ether). Yield of **6** (colorless oil) 47.0 g (73%). ^{1}H NMR ($CDCl_3$): δ 3.60 (t, 2H, CH_2OH), 3.35 (t, 2H, CH_2Br), 1.40 (m, 16H) ppm.

5.1.2. 2-(10-Bromo-decyloxy)-tetrahydropyran 7. To a cooled (0 °C) solution of 10-bromo-decan-1-ol **6** (27.5 g 116 mmol) in dichloromethane (100 mL) a small amount of *p*-TsOH was added, followed by dropwise addition of dihydropyran (10 g, 119 mmol). The reaction mixture was stirred for 2 h, diluted with diethyl ether and washed with

aqueous $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (hexane–ether 6:1) giving 35.17 g of product **7** (94%). ^{1}H NMR ($CDCl_3$): δ 4.50 (m, 1H, OC*H*O, 3.60 (m, 4H, 2×CH_2–O), 3.35 (t, 2H, CH_2Br), 1.40 (m, 22H) ppm. This material was used in the next step.

5.1.3. 13-(Tetrahydropyran-2-yloxy)-tridec-2-yn-1-ol 8. Ammonia (250 mL) was condensed in a 500 mL 3-necked flask. The temperature was kept between −40 and −50 °C with dry ice/*i*-PrOH and 0.025 g of Li metal was added to the ammonia giving a blue color on dissolution. The reaction mixture was kept under nitrogen and stirred magnetically. After addition of a small amount of $Fe(NO_3)_3{\cdot}9H_2O$ the formation of $LiNH_2$ was catalyzed and could be observed by the change of color (blue to grey). Finely cut pieces of Li (2.17 g, 312 mmol) were added slowly. The initially blue color on addition of the Li, eventually turned into a white-greyish one. A solution of propargyl alcohol (8.74 g, 156 mmol) in THF (40 mL) was then added dropwise. The resulting mixture was stirred for another hour after which a solution of the bromide **7** (16.71 g, 52 mmol) in THF (70 mL) was added. Stirring was continued for 1.5 h at −40 °C and the reaction mixture was left overnight at ambient temperature resulting in complete evaporation of the ammonia. The residue was cautiously treated with water (120 mL) and then extracted with ether (3×80 mL). The organic layer was washed with water and dried ($MgSO_4$). After work-up 15.3 g of crude material (99.3%, purity according to GLC 92.2%) was obtained. This crude material was pure enough for further use. A small amount (5.0 g) was purified further via chromatography over silica gel (eluent hexane–CH_2Cl_2 1:1, followed by CH_2Cl_2–AcOEt 1:1), giving 4.46 g of pure product according to GC. IR (neat): ν_{max} 3390 (OH), 2280, 2220 (C≡C) cm^{-1}. ^{1}H NMR (400 MHz): δ 4.58 (1H, m, O–C*H*–O), 4.24 (2H, s, CH_2OH), 3.87 (1H, m, CH*H*–O, THP-ether ring), 3.72 (1H, m, O–CH*H*, alkyl chain), 3.51 (1H, m, C*H*H–O, THP-ether ring), 3.39 (1H, m, O–C*H*H, alkyl chain), 2.18 (2H, m, CH_2–C≡), 1.90 (1H, br s, O*H*), 1.85 (1H, m), 1.70 (1H, m), 1.61–1.48 (8H, m), 1.36–1.28 (12H, m) ppm. ^{13}C NMR: signals at 98.78, 86.41, 78.37, 67.64, 62.25, 51.26, 30.73, 29.68, 29.43, 29.37, 29.35, 29.02, 28.77, 28.56, 26.16, 25.47, 19.61 and 18.68 ppm. Mass spectrum (EI) peak match for M^+ (abundancy.8%) calcd for $C_{18}H_{32}O_3$, 296.2352; found: 296.2344. Peak match for M^+-CH_2OH (abundancy 3.5%) calcd for $C_{17}H_{29}O_2$ 265.2168; found: 265.2166.

5.1.4. 13-(Tetrahydropyran-2-yloxy)-tridec-2-en-1-ol 9. A mixture of diethyl ether–THF (650 mL, ratio 7:8), was added to LAH (7.6 g, 0.2 mol). The suspension was stirred magnetically, kept under nitrogen and cooled below −65 °C. A solution of the alkynol **8** in diethyl ether–THF (400 mL, 7:8) was added slowly; the temperature was kept below − 60 °C. After the addition the temperature of the reaction mixture was allowed to rise to room temperature, then the temperature was raised to 35–40 °C and maintained at this level during 12 h. The reaction mixture was decomposed by careful addition of water at −10 °C. The colorless $Al(OH)_3$ was filtered off and the filtrate was dried ($MgSO_4$). Work-up gave the product as a slightly colored viscous oil (29.86 g, quant.). This crude product could be used as such in the next step. A small amount was purified by chromatography for further analysis. IR (neat): ν_{max} 3360 (OH), 1662 (C=C) cm^{-1}. NMR (400 MHz) ($CDCl_3$): δ 5.73–560 (2H, m, *H*C=C*H*), 4.57 (1H, m, O–C*H*–O), 4.07 (2H, m, CH_2OH), 3.86 (1H, m, CH*H*–O, THP ring), 3.71 (1H, d t, C*H*H–O, chain), 3.49 (1H, m, C*H*H–O, THP ring), 3.38 (1H, dt, CH*H*–O, chain), 2.03 (2H, m, C–CH_2–C=C), 1.84 (1H, m), 1.70 (1H, m) 1.60–1.27 [21H, m, (CH_2)$_8$+(CH_2)$_2$+OH] ppm. ^{13}C NMR: 133.4, 128.9 (alkene C), 98.8 (acetal C), 67.7, 63.7, 62.3 (*C*–O), further methylene ^{13}C absorptions at 32.16, 30.77, 29.73, 29.51, 29.48, 29.42, 29.36, 29.11, 29.10, 26.20, 25.48, 19.65 ppm. Mass spectrum (EI), peak match at M^+ calcd for $C_{18}H_{34}O_3$: 298.2508; found: 298.25085. Peak match at M−85, calcd for $C_{13}H_{25}O_2$: 213.1855; found: 213.1855.

The by-product (the allene, 2-trideca-11,12-dienyloxy-tetrahydro-pyran) was isolated by chromatography over silica gel (CH_2Cl_2). IR (neat): ν_{max} 3040 (=CH_2), 1950 (C=C=C) cm^{-1}. ^{1}H NMR (90 MHz): δ 5.08 (1H, appearing as quintet, C*H*–C=C), 4.73–4.47 (3H, q+m, O–C*H*–O+C=C=CH_2), 4.03–3.2 (4H, 2×CH$_2$, CH_2–O–C), 2.16–1.07 [24H, m, CH_2–C=+(CH_2)$_8$+(CH_2)$_3$] ppm.

5.1.5. (2*R*,3*R*)-2,3-Epoxy-13-(2-tetrahydropyran-yloxy)-tridecan-1-ol 10. A solution of Ti(O*i*Pr)$_4$ (29.00 g, 102 mmol) in dichloromethane (650 mL) was cooled to −30 to −40 °C. D-(−)-Diethyl tartrate (21.03 g, 102 mmol) dissolved in dichloromethane (100 mL) was added in one portion. The resulting solution was stirred for 5 min at the low temperature and then allylic alcohol **9** (29.80 g, 100 mmol) was added. After stirring for another 5 min a solution of *tert*.-butyl hydroperoxide (50 mL, 4.1 mol) in dichloroethane was added. The reaction mixture was left overnight at −25 °C. A 10% aqueous tartaric acid solution (300 mL) was added slowly and the mixture was stirred at −10 °C for 30 min and for 1 h at room temperature. A clear yellow mixture was obtained, the organic layer was washed with water (3×) and dried over $MgSO_4$. The solvent was evaporated and the residue was dissolved in diethyl ether (400 mL). The solution was cooled to 0 °C and stirred with 1 N NaOH (400 mL) for 30 min. The ether layer was washed once with water and dried over Na_2SO_4. Evaporation of the solvent and removal of remaining *t*-BuOOH in vacuo gave the crude product (28.30 g). This material was stored and purified in portions when needed.

Crude epoxy alcohol **10** (6.30 g) was chromatographed over 130 g of silica gel. Elution with EtOAc–hexane (2:1) gave 0.48 g of allene and 0.22 g of starting material. Elution with EtOAc–hexane (1:1) gave 4. 33 g of pure epoxy alcohol as an oil (68.7%). $[\alpha]_D^{20}$=+18 ($CHCl_3$, *c*=0.5). IR: ν_{max} 3420 (OH) cm^{-1}. ^{1}H NMR (400 MHz) ($CDCl_3$): δ 4.57 (1H, m, O–C*H*–O), 3.92–3.84 (2H, m, C*H*H–OH+C*H*H–O THP-ring), 3.73 (1H, dt, O–C*H*H–CH$_2$, alkyl chain), 3.62 (1H, dd, CH*H*OH), 3.38 (1H, m, CH*H*–O THP-ring), 3.38 (1H, dt, O–CH*H*–CH$_2$, alkyl chain), 2.96–2.90 (2H, m, *H*C–O–C*H*), 1.71 (1H, m), 1.63–1.28 (25H, m) ppm. ^{13}C NMR: δ 98.87 (*C* acetal), 67.69 (O–*C*H$_2$ alkyl chain), 62.34 (*C*H$_2$–O, THP-ring), 61.77 (*C*H$_2$–OH), 58.34 (CH$_2$*C*H, epoxy), 55.99 (CH–O–*C*H–CH$_2$OH), further methylene C absorptions at 31.55, 30.82, 29.76, 29.51, 29.47, 29.44, 29.36, 26.23, 25.92, 25.54, 19.71 ppm, one ^{13}C absorption

was missing due to overlap of two signals. MS, peak match M^+, calcd 314.2457; found: 314.2453.

Another purification of crude epoxy alcohol (13.25 g) gave a product (9.90 g) with a purity of 95.6% according to GC (75.2% yield calcd on allylic alcohol **9**).

5.1.6. (2*S*,3*R*)-2,3-Epoxy-13-(2-tetrahydro-pyran-yloxy)-tridecan-1-al. To a magnetically stirred solution of oxalyl chloride (3.30 g, 26 mmol) in dichloromethane (50 mL), cooled at −60 °C and kept under nitrogen, was added dropwise a solution of DMSO (2.73 g, 35.0 mmol) in dichloromethane (20 mL). A solution of the epoxy alcohol **10** (5.41 g, 17.2 mmol) in dichloromethane (30 mL) was added and the mixture was stirred for 15 min. Then, triethylamine (12 mL) was added and the mixture was allowed to warm-up to room temperature. Water (100 mL) was added and the two layers were separated. The dichloromethane layer was washed once more with water, and dried ($MgSO_4$). Evaporation of the solvent gave crude epoxy aldehyde (5.4 g) as a yellow colored oil. Purity according to GLC: 88.6%. NMR (90 MHz) ($CDCl_3$): δ 9.0 (1H, d, C*H*═O), 4.55 (1H, m, O−C*H*−O), 4.0–3.0 (6H, m, 2×CH_2O+C*H*−O−C*H*), 2.0–1.0 [24H, m, (CH_2)$_9$+(CH_2)$_3$] ppm. This aldehyde was used immediately for the next step.

5.1.7. (3*S*,4*R*)-1-Diazo-3,4-epoxy-14-(2-tetrahydropyran-yloxy)-tetradecan-2-one 12. The crude epoxy aldehyde (5.4 g, assumed 17.2 mmol) was dissolved in *t*-BuOH (200 mL). Isobutene (75 mL) was added as chlorine scavenger. At room temperature a solution of $NaClO_2$ (12 g, 133 mmol) and NaH_2PO_4 (12 g, 100 mmol) in water (120 mL) was added dropwise. The resulting mixture was left overnight at room temperature. Evaporation of the more volatile compounds gave an oily compound in the water layer. The oil was extracted with diethyl ether (4×40 mL) and the solution was dried over $MgSO_4$. Evaporation of the solvent gave the glycidic acid **11** as a crude oil in quantitative yield. This product was used for the next reaction immediately.

To an ice-cooled solution of the crude glycidic acid (5.37 g) in diethyl ether (60 mL) was added iso-butyl chloroformate (2.60 g, 19.0 mmol). This was followed by addition of a solution of Et_3N (2.26 g, 22.4 mmol) in diethyl ether (20 mL). After stirring for 30 min, the precipitated salt was filtered off and the filtrate was added to an ethereal diazomethane solution (143 mL, 0.3 mol) that was cooled at −30 °C. The mixture was left overnight at room temperature and excess diazo methane was removed by a stream of nitrogen. Some additional Et_3N·HCl salt was removed by filtration and the filtrate was concentrated. A yellow oil remained (5.88 g), that was purified by chromatography over 90 g of silica gel. Elution with hexane–EtOAc 4:1 yielded the pure epoxy diazomethyl ketone **12** (4.00 g, 68% calculated on the epoxy alcohol) as a yellow oil. $[\alpha]_D^{20}$=−43.1 ($CHCl_3$, *c*=1). IR (neat): ν_{max} 3115 (CH═), 2940, 2860 (aliph CH_2), 2110 (═N═N), 1640 (C═O) cm^{-1}. ^{1}H NMR (C_6D_6, 400 MHz): δ 4.75 (1H, s, C*H*═N_2), 4.62 (1H, m, appears as t with *J*=3.0 Hz, O−C*H*−O), 3.87–3.82 (2H, m, CH_2−O), 3.44–3.35 (2H, m, CH_2O), 3.04 (1H, d, *J*=2 Hz, O−C*H*−C═O), 2.56 (1H, bs, CH_2−C*H*−O, epoxide), 1.79 (1H, m), 1.65–1.61 (4H, m) 1.42–1.02 (19H, m) ppm. ^{13}C NMR: 190.45 *C*═O, 98.70 O−*C*H−O, 67.56 *C*H_2−O, 61.69 *C*H_2−O, 58.93 *C*−C═O, epoxide, 58.66 *C*−CH_2, epoxide, 50.63 *C*H−N_2, further methylene carbon absorptions at 31.77, 31.15, 30.31, 29.94, 29.86, 29.80, 29.73, 29.63, 29.48, 26.79, 26.00, 19.75 ppm. MS, EI$^+$ 352 (M^+) 0.3%, 351 (M^+-1) 0.7%, 269 (M^+-83) 8.6%, 101 ($C_5H_9O_2^+$) 71%, 85 ($C_5H_9O^+$) 100%.

5.1.8. (4*R*)-4,14-Dihydroxy-tetradec-2-enoic acid ethyl ester 13. A solution of epoxy diazomethyl ketone **12** (3.84 g, 10.9 mmol) in EtOH (1050 mL) was irradiated in a Pyrex tube at 300 nm. The progress of the reaction was followed by IR. After 4 h the diazo absorption had vanished, and the solvent was evaporated leaving 3.12 g of an oil. According to GLC this product was 80% pure. According to NMR the product had lost its THP protecting group. IR (CCl_4): ν_{max} 3620 (sharp, OH), 3500 (br, OH), 2940, 2860 (aliphatic CH_2), 1740 (EtO−C═O), 1660 (C═C), cm^{-1}. ^{1}H NMR (90 MHz) ($CDCl_3$): δ 6.95 (1H, dd, *J*=16 Hz, *J*=5.5 Hz, *H*C═C−C═O), 6.02 (1H, dd, *J*=16, 2 Hz, C═C*H*−C═O), 4.17 (3H, q, *J*=7 Hz, O−C$H_2$$CH_3$ and C*H*−OH), 3.60 (2H, t, *J*=6 Hz, CH_2−OH), 2.92 (2H, m, O*H*), 1.8–1.1 [21H, m, (CH_2)$_9$+CH_3] ppm. The product was used in the next step right away.

5.1.9. (4*R*)-4,14-Dihydroxy-tetradecanoic acid ethyl ester 14. $Ni(OAc)_2$·$4H_2O$ (1.43 g, 5.8 mmol), was suspended in EtOH (50 mL) and transferred to a hydrogenation flask. A 1 mol solution of $NaBH_4$ (6 mL) in EtOH was added, giving a black suspension. A solution of the γ-hydroxy-α,β-unsaturated ester **13** (3.12 g, when pure 10.9 mmol) in EtOH (50 mL) was added. The device was connected to a hydrogen supply and the uptake of hydrogen at normal pressure was measured. After uptake of 225 mL of hydrogen the reaction mixture was filtered through celite. The solvent was evaporated and the residue purified by chromatography over silica gel (100 g). Elution with hexane–EtOAc 3:1, which was gradually changed to 1:1 gave the desired compound **14** as colorless fluffy needles (1.77 g, 57%, calcd on epoxy diazomethyl ketone). After recrystallization from hexane–CH_2Cl_2: mp 48–50 °C. IR ($CHCl_3$): ν_{max} 3600, 3450 (OH), 1765 (sh, C═O), 1720 (C═O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.13 (2H, q, *J*=7.5 Hz, O−C$H_2$$CH_3$), 3.60 (3H, t+m, t *J*=5 Hz, HO−CH_2,+C*H*−OH), 2.43 (2H, t, *J*=7.5 Hz, CH_2C═O), 2.2 (2H, b s, 2×O*H*), 1.8–1.1 [23H, m, (CH_2)$_9$+CH_2+CH_3) ppm. Elemental analysis for $C_{16}H_{32}O_4$ (288.431), calcd, C: 66.63; H 11.18%; found: C: 66.59; H: 11.05%.

5.1.10. (5*R*)-5-(10-Hydroxydecyl)-dihydrofuran-2-one 15. A solution of the dihydroxy ester **14** (1.40 g, 4.85 mmol) in benzene (80 mL) containing a small amount of TsOH, was heated at reflux for 2 h. The reaction was monitored by TLC. The reaction mixture was washed with aq. $NaHCO_3$ and water. Work-up gave compound **15** (1.18 g, quant.) as colorless crystals (mp 80–81 °C). $[\alpha]_D^{20}$=+23.9 ($CHCl_3$, *c*=0.8). IR ($CHCl_3$): ν_{max} 3600, 3470 (OH), 1765 (C═O), cm^{-1}. ^{1}H NMR (400 MHz) δ 4.48 (1H, m, C*H*OC═O), 3.64 (2H, t, *J*=6.5 Hz, CH_2OH), 2.52 (2H, m, CH_2−C═O), 2.32 (1H, m, C*H*H−CH_2−C═O), 1.71 (1H, m, CH*H*−CH_2−C═O)1.60–1.23 [19H, m, (CH_2)$_9$+O*H*] ppm. ^{13}C 177.15 *C*═O, 81.00 *C*H−O, 63.01 *C*H_2OH, *C*H_2 peaks at 35.56, 32.76, 29.52, 29.47,

29.34, 29.26, 27.96, 26.18, 25.50, 25.42 and 25.16 ppm. Elemental analysis for $C_{14}H_{26}O_3$ (242.360): calcd, C: 69.38; H: 10.81%; found: C: 68.66; H: 10.81%.

5.1.11. (5*R*)-5-[10-(2-Tetrahydropyran-yloxy)]-decyl-dihydrofuran-2-one 37. The alcohol function of compound **15** was reprotected as follows: to a solution of alcohol **15** (435 mg, 1.8 mmol) in CH_2Cl_2 (10 mL) cooled at 0 °C, a solution of dihydropyrane (160 mg, 1.9 mmol) in CH_2Cl_2 (2 mL) was added. A small amount of TsOH was added as catalyst. After 1 h at room temperature the solution was washed with satd bicarbonate solution and dried over $MgSO_4$. Work-up and chromatography over silica gel (hexane–EtOAc 2:1) gave product **37** as a slightly yellow oil (500 mg, 85%). $[\alpha]_D^{20}=+20.6$ ($CHCl_3$, $c=0.6$). ^{1}H NMR (400 MHz) ($CDCl_3$): δ 4.57 (1H, m, O–C*H*–O), 4.48 (1H, m, C*H*–O–C=O), 3.87 (1H, m, C*H*H–O THP-ring), 3.73 (1H, m, C*H*H–O, chain), 3.52 (1H, m, CH*H* THP-ring), 3.38 (1H, m, CH*H*–O, chain), 2.52 (2H, m, CH_2–C=O), 2.32 (1H, m, C*H*H–CH_2–C=O), 1.84 (1H, m, CH*H*–CH_2–C=O), 1.8–1.28 [24H, m, $(CH_2)_3$+$(CH_2)_9$)] ppm. ^{13}C NMR: 177.05 *C*=O, 98.84 O–*C*H–O, 80.95 *C*H–O–C=O, 67.64 O–*C*H_2 chain, 62.31 O–*C*H_2 THP-ring, other *C*H_2 peaks at 35.55, 32.76, 30.77, 29.71, 29.47, 29.39, 29.37, 29.27, 28.78, 27.95, 26.18, 25.49, 25.16, 19.67 ppm.

5.1.12. (5*R*)-5-[10-(2-Nitro-phenylselanyl)-decyl]-dihydrofuran-2-one 16. To a magnetically stirred solution of alcohol **15** (754 mg, 3.11 mmol) and *o*-nitrophenyl-selanyl cyanide (1181 mg, 5.20 mmol) in THF (25 mL) was added at room temperature a solution of Bu_3P (1296 μL, 5.20 mmol) in THF (10 mL). The reaction was followed by TLC. After 2 h the reaction was complete and the deeply reddish-brown colored solution was concentrated. The residue was subjected to column chromatography over silica gel, eluent EtOAc–hexane 1:3→1:2. This gave yellow crystals (1186 mg, 93%) of compound **16**. IR ($CHCl_3$): ν_{max}1760 (C=O), 1590 (Ar), 1500, 1335 (NO_2). ^{1}H NMR ($CDCl_3$): δ 8.23 (1H, d, J=8.0 Hz, C*H*=C–NO_2), 7.6–7.0 (3H, m, Ar*H*), 4.48 (1H, m, C*H*–OC=O), 2.90 (2H, t, J=7.5 Hz, CH_2Se), 2.7–1.1 [22H, m, $(CH_2)_9$+$(CH_2)_2$] ppm. This material was processed immediately in the next step.

5.1.13. (5*R*)-5-(Dec-9-enyl)-dihydrofuran-2-one 17. To a solution of the selenide **16** (532 mg, 1.25 mmol) in THF (15 mL) at a temperature of 5 °C was added hydrogen peroxide (1.5 mL 30%, 13 mmol). The reaction mixture was stirred for 3.5 h at room temperature. At this point very little starting material remained. After 5 h the starting material was consumed completely. Then, hexane (50 mL) was added. A satd aqueous solution of $NaHCO_3$ (50 mL) was added and the mixture was stirred vigorously. The aqueous layer was extracted twice with hexane (40 mL). The combined organic layers were dried over $MgSO_4$. Work-up and purification by chromatography over silica gel (30 g), eluent EtOAc–hexane 1:5, gave compound **15** (190 mg, 68%) as a yellow oil. The yellow color is due to a small trace of a selenide contaminant. According to GLC the purity was >95%. IR (neat): ν_{max} 3060 (C=CH), 1770 (C=O), 1640 (C=C) cm^{-1}. ^{1}H NMR: δ 6.23–5.33 (1H, m, H_2C=C*H*), 5.3–4.7 (2H, m, *H*$_2$C=C), 4.47 (1H, m, C*H*–OC=O), 2.7–1.1 [20H, m, $(CH_2)_8$+$(CH_2)_2$] ppm. This material was coupled with **18** without further purification.

5.1.14. (3*R*/*S*,5*R*)-5-Dec-9-enyl-3-{[(4*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-hydroxy-methyl}-dihydrofuran-2-one 19/20. To a LDA solution [prepared from *i*Pr_2NH (303 mg, 3 mmol) and BuLi (2 mL of 1.6 molar sol. in hexane)] in THF (5 mL) while kept at −70 °C, was slowly added a solution of the lactone **15** (448 mg, 2 mmol) and DMPU (320 mg, 2 mmol) in THF (5 mL).The reaction mixture was stirred for 15 min at this temperature and then a solution of (4*R*)-2,2-dimethyl-[1,3]-dioxolane-4-carbaldehyde **18** (781 mg, 6.0 mmol) in THF (5 mL) was added in one portion. The reaction mixture was kept at −70 °C for 6 h. The reaction was quenched with satd aqueous NH_4Cl and the mixture was extracted with ether. After drying ($MgSO_4$), work-up gave an oil that was purified by column chromatography over 40 g of silica gel. Elution with CH_2Cl_2 gave starting material (40 mg, 9%). With diethyl ether the product (650 mg, 91%) was obtained as a mixture of two isomers **19/20** (according to GLC). By careful crystallization (diethyl ether–hexane) one of the alcohols was isolated in pure form (mp 60–62 °C). A mass spectrum (CI) showed the M^{+1} peak at 355. IR (CCl_4): ν_{max} 3600 (OH, w), 3500–3400 (OH, m, b), 3080 (=CH, w), 2990, 2930, 2860 (aliphatic hydrogens) 1760 (C=O, s), 1640 (C=C, w), 1380, 1370 (typical absorptions of the dioxolane function, cm^{-1}. ^{1}H NMR (90 MHz FT) ($CDCl_3$): δ 6.2–5.6 (1H, m, *H*C=CH_2), 5.15–4.8 (2H, m,=C*H*$_2$), 4.75–4.4 (1H, m, C*H*OC=O), the remaining part of the spectrum contained several signals, however, the resolution was to poor to allow a reliable assignment. The mixture of **19/20** was used as such in the next step.

5.1.15. Reaction of alcohol 19/20 with *N*,*N*′-thiocarbonyldiimidazole. *At room temperature*. To a solution of the alcohol mixture of **19/20** (350 mg, 1.0 mmol) in THF (5 mL) was added *N*,*N*′-thiocarbonyldiimidazole (350 mg, 2 mmol) at room temperature. The reaction mixture was stirred for 6 h at this temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed over 30 g of silica gel with hexane–EtOAc 2:1. A small amount of conjugated unsaturated product **23**+**24** (20 mg, 6%) was eluted first, followed by fractions with starting material (73 mg, 21%), and the desired thiocarbonyl-imidazolide mixture **21** (an oil, 298 mg, 64. IR (CCl_4): ν_{max} 3160 (w), 3145 (w), 3075(w,=CH), 2995, 2925, 2860 (aliphatic CH_2), 1770 (C=O), 1640 (=CH_2), 1380, 1370 (typical absorptions of dioxolane), cm^{-1}. ^{1}H NMR (CCl_4): δ 8.2, 7.6, 6.9, 3×s of imidazole ring. The proton at the carbon with the imidazolide substituent was present as a multiplet at 5.8 ppm. No further assignments were made.

In THF at reflux temperature. A solution of the alcohol mixture **19/20** (177 mg, 0.5 mmol) and *N*,*N*′-thiocarbonyl-diimidazole (178 mg, 1 mmol) in dry THF (10 mL) was refluxed for 3 h. Still some starting material **19/20** was left. Another portion of *N*,*N*′-thiocarbonyldiimidazole (45 mg, 0.25 mmol) was added and heating at reflux temperature was continued for 1 h. The solvent was evaporated and the residue was chromatographed over silica gel (hexane–EtOAc 2:1). The conjugated unsaturated products **23**+**24** were obtained first (37 mg, 22%), followed by starting material (34 mg, 20%) and the desired product **21** as an oil (128 mg, 55%). The

imidazolides **21** were used in the next step without further characterization.

5.1.16. (3*R*/*S*,5*R*)-5-Dec-9-enyl-3-[(4*S*)2,2-dimethyl-[1,3]-dioxolan-4-yl]-methyl-dihydrofuran-2-one 22. To a solution of thiocarbonyldiimidazoles **21** (90 mg, 0.19 mmol) in toluene (10 mL) was added freshly prepared tributyltin hydride (125 mg, 0.43 mmol). The solution was slowly heated to reflux temperature, at which point the reaction was complete. After removal of the solvent, the residue was purified by flash chromatography (EtOAc–hexane 1:4) over silica gel. This afforded product **22** as an oil (45 mg, 70%). According to GLC two isomers were present. IR (neat): ν_{max} 3070, 2980, 2920, 2850, 1770, 1640, 1380, 1370 cm^{-1}. ^1H NMR (90 MHz) ($CDCl_3$): δ 6.1–6.5 (1H, m, *H*C=CH_2), 5.2–4.85 (2H, m, C*H*$_2$=CH), 4.80–4.0 (2H, m, 2×C*H*–O), 4.0–3.3 (2H, m, C*H*$_2$–O) ppm, the remaining signals could not be assigned. This material was used as such in the next deprotection step.

5.1.17. (3*S*,5*R*,2′*S*)-5-Dec-9″-enyl-3-(2′,3′-dihydroxy-propyl)-dihydrofuran-2-one 25 and (3*R*,5*R*,2′*S*)-5-dec-9″-enyl-3-(2′,3′-dihydroxy-propyl)-dihydrofuran-2-one 26. Product **22** (45 mg) was dissolved in a small amount of MeOH (5 mL) and TosOH (50 mg) was added. After stirring for 1 h at room temperature hydrolysis was complete. The solvent was evaporated and the residue dissolved in diethyl ether. After washing with bicarbonate solution, the organic phase was dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by flash chromatography over silica gel (EtOAc–hexane 2:1). This gave 20 mg of product (61%). It was pure according to TLC and GLC. However, a long melting range was observed starting at 65 °C. A 400 MHz ^1H NMR spectrum in $CDCl_3$ showed signals of two products. Compound **25**: δ 5.80 (m), 4.94 (m), 4.38 (m), 3.98 (m), 3.68 (m), 3.49(m), 2.84 (m), 2.54 (m), 2.03–1.28 (m) ppm. Compound **26**: δ 5.80 (m), 4.94 (m), 4.60 (m), 3.82 (m), 3.65 (m), 3.55 (m), 2.91 (m), 2.18 (m), 2.03–1.28 (m) ppm. The ratio of **25**/**26** was 2:3.

5.1.18. Reaction of thiocarbonylimidazolide 21 with tributyltin hydride in toluene at reflux temperature. A solution of the imidazolide **21** (crude 840 mg, 1.8 mmol) in toluene (20 mL) was added dropwise to a solution of tributyl tinhydride (1.16 mL, 4.0 mmol) in toluene (20 mL) which was heated at reflux. The mixture was heated at reflux for another hour. After cooling, the solvent was evaporated under reduced pressure and the residue was chromatographed over silica gel (45 g). Eluting with hexane–EtOAc 4:1, followed by hexane–EtOAc 2:1. The first fraction (50 mg, 8%) was the pure conjugated *Z*-alkene **23**. IR (CCl_4): ν_{max} 3070 (w, =CH), 2990, 2920, 2850 (s, aliphatic CH_2 and CH_3), 1755 (s, C=O), 1675 (w, C=C conjugated), 1640 (w,=CH_2) 1380, 1370 (dioxolane absorptions) cm^{-1}. ^1H NMR: δ 6.20 (1H, dt, J=8 Hz, J=1.5 Hz, O=C–C=C*H*), 6.05–5.50 (2H, m, CH_2=C*H*, C=CH–C*H*–O), 5.1–4.75 (2H, m,=C*H*$_2$), 4.6–4.0 (2H, m, C*H*O–C=O, C*H*H–O), 3.75–3.40 (1H, m, CH*H*–O), 3.15–2.15 (2H, dq, J=18 Hz, J=7.0 Hz, and an allylic coupling of 1.5 Hz, lactone C*H*$_2$), 2.15–1.8 (2H, m,=CH–C*H*$_2$), 1.8–0.6 (rest of protons, m) ppm. The next fraction gave a colorless oil (339 mg, 56%). which consisted of a mixture of the *E* and *Z*-isomers **24** and **23**, in equal amounts according to GC. Another chromatographic purification with hexane–EtOAc as eluent gave also a small amount of *E*-isomer **24**. IR (CCl_4): ν_{max} 3070 (w, =CH), 2990, 2920, 2850 (s, aliphatic CH_2 and CH_3), 1750 (s, C=O), 1670 (w, C=C–C=O), 1640 (w, C=C), 1380, 1370 (dioxolane absorptions) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.66 (1H, dt, J=8 Hz, J=1.8 Hz, O=C–C=C*H*), 6.1–5.6 (1H, m, H_2C=C*H*), 5.15–4.8 (2H, m,=C*H*$_2$), 4.9–4.3 (2H, *H*C–O–C=O,=C–C*H*–O), 4.3–4.1 (1H, s, H*H*C–O), 3.9–3.6 (1H, m, *H*HC–O), 3.25–2.45 (2H, dq, C*H*$_2$ lactone+allyl coupling), 2.2–1.9 (2H, m, =CH–C*H*$_2$), 1.95–1.0 (the remaining protons as broad multiplet) ppm.

5.1.19. (3*S*,5*R*,4′*S*)-5-Decyl-3-(2′,2′-dimethyl-[1′,3′]-dioxolan-4′-yl)-methyl-dihydrofuran-2-one 27. A mixture of the two isomeric alkenes **23**+**24** (20 mg) was dissolved in EtOH (10 mL) and hydrogenated over Pd/C catalyst at room temperature at normal pressure. After 2 h the mixture was filtered over hyflo and the filtrate concentrated. This gave a single compound **27** (18 mg), according to GC, as an oil that crystallized on standing. Recrystallization from hexane gave a solid, mp 38–41 °C. (mp of acetonide of rubrenolide 47–48 °C). IR (CCl_4): ν_{max} 2995, 2940, 2860 (s, CH_2, CH_3), 1770 (s, C=O), 1470, 1455 (m), 1380, 1370 (s), 1170 (s) cm^{-1}. ^1H NMR (90 MHz, FT) ($CDCl_3$): δ 4.5–4.2 (1H, m, C*H*OC=O), 4.2–4.0 (2H, m, C*H*$_2$O), 3.7–3.4 (1H, m, C*H*–O–CH_2–O), 2.9–2.35 (2H, m), 2.3–2.0 (1H, m), 1.9–1.2 (remaining protons as multiplet, with singlets of C*H*$_3$ at 1.38 and 1.32), 0.88 (3H, broad triplet, CH_2–C*H*$_3$) ppm.

5.1.20. Epi-dihydro-rubrenolide 28. Acetonide **27** (5 mg) was treated with *p*-TsOH in MeOH (1 mL). Almost immediate hydrolysis of the acetonide function took place. A small amount of satd aq. $NaHCO_3$ soln was added and the mixture was extracted with ether. After drying and removal of the solvent a solid was obtained. Recrystallization from ether–hexane gave fine needles, mp 94–96 °C. IR (KBr): ν_{max} 3450 (OH), 2995, 2945, 2860 (CH_2, CH_3), 1745 (C=O) cm^{-1}. ^1H NMR (400 MHz) (CD_3OD): δ 4.46 (1H, m, C*H*O–C=O), 3.88 (1H, m, HO–C*H*–CH_2–OH), 3.51 (2H, m, C*H*$_2$–OH), 2.90 (1H, m, C*H*–C=O), 2.60 (1H, m, lactone ring H*H*C–C–O–C=O), 2.06 (1H, m, C*H*H of dihydroxy-propyl side chain), 1.74 (1H, m, CH*H* of dihydroxy-propyl side chain), 1.7–1.3 (19H, m), 0.9 (3H, t, J=7 Hz, CH_2–C*H*$_3$) ppm.

For comparison the ^1H NMR spectrum of dihydrorubrenolide obtained through hydrogenation of natural rubrynolide is given. ^1H NMR (400 MHz) (CD_3OD): δ 4.40 (1H, m, C*H*–O–C=O), 3.60 (1H, m, HO–C*H*–CH_2–OH), 3.49 (2H, dd, C*H*$_2$–OH), 2.94 (1H, m, C*H*–C=O), 2.54 (1H, ddd, lactone ring H*H*C–C–O–C=O, α H), 1.92 (1H, ddd, C*H*H of dihydroxy-propyl side chain), 1.70 (1H, m, CH*H* of dihydroxy-propyl side chain), 1.60 (1H, m, lactone ring *H*HC–C–O–C=O, βH), 1.6–1.25 (remaining protons), 0.90 (3H, t, J=7 Hz) ppm. This spectrum clearly differs from that of **28**.

5.1.21. Tridec-2-yn-1-ol.[31] 1-Bromotridecane (20.0 g, 91 mmol), propargylic alcohol (14.84 g, 264 mmol) and $LiNH_2$ (from 3.6 g of Li, 514 mgat) in ammonia (100 mL) was brought in reaction as described for compound **8**. After

1.5 h DMSO (15 mL) was added and the reaction mixture was left overnight After work-up the oil obtained was purified by destillation b.p. 94–95 °C (0.05 Torr), yield 16.0 g (90%). The oil solidified on standing, lit. mp 37–38 °C. IR (CCl_4): ν_{max} 3620 (OH), 2280, 2220 (alkyn) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.2–4.4 (2H, bs, $-CH_2OH$), 2.1–2.3 (2H, m, $CH_2C\equiv$), 1.2–1.7 [16H, m, $(CH_2)_8$)], 0.9 (3H, t, CH_2CH_3) ppm.

5.1.22. *E*-Tridec-2-ene-1-ol. To a suspension of $LiAlH_4$ (10.0 g, 262 mmol) in diethyl ether (75 mL) that was cooled with an ice-salt bath, a solution of tridec-2-yn-1-ol (25.7 g, 130 mmol) in diethyl ether (75 mL) was added over a period of 2.5 h. Then THF (170 mL) was added and the mixture was heated at reflux for 2.5 h. After cooling in ice a few mL of water were added carefully to hydrolyse the Li/Al salts. A white solid was formed and the mixture was dried over $MgSO_4$. Work-up gave a light-yellow oil that solidified on standing at 0 °C (23.45 g). This alkene was contaminated with the allene (15%) according to GC and it was used as such for the next reaction.

5.1.23. (2*R*,3*R*)-2,3-Epoxy-tridecane-1-ol 29.[32] To a magnetically stirred suspension of molsieves (1.51 g, 4 Å) in dichloromethane (175 mL), while kept at −20 °C, D(−)-DET (625 mg, 3.0 mmol) and $Ti(OiPr)_4$ (.72 g, 2.5 mmol) were added. After slow addition (1 h) of TBHP (25 mL of a 4.08 molar solution in dichloroethane, 100 mmol) the slightly yellow solution was stirred at −20 °C for 30 more minutes. A solution of tridec-2-ene-1-ol (10 g, 50.5 mmol) in dichloromethane was added over a period of 1 h. The reaction mixture was kept at −20 °C for 3 h. The temperature was allowed to rise to 0 °C and the reaction mixture was then poured into a solution of ferrosulfate (16 g, 60 mmol) and tartaric acid (5.0 g, 30 mmol) in water (50 mL). After stirring vigorously for 15 min the two layers were separated. The water layer was extracted with ether (2×75 mL) and the organic layers were stirred with a solution of NaOH (30%, 25 mL, satd with NaCl, kept at 0 °C). After stirring at 0 °C for 45 min, water (250 mL) was added and the layers were separated. The water layer was extracted once more with ether (150 mL) and the organic phase was dried over $MgSO_4$. Work-up afforded a colorless solid (8.93 g, 77%). Chromatography (EtOAc–hexane 1:3) over silica gel gave the pure compound (7.5 g, 69%), $[\alpha]_D^{20}$=+25 ($CHCl_3$, c=1). Lit.[32] $[\alpha]_D$ of the 2*S*,3*S* compound −24 ($CHCl_3$). IR (CCl_4): ν_{max} 3600 (OH) cm^{-1}. ^1H NMR (90 MHz) (CCl_4): δ 4.40–3.4 (2H, m, CH_2–OH), 3.0–2.8 (2H, m, *H*C–C*H*), 1.8–1.2 [(18H, m, $(CH_2)_9$], 0.9 (3H, t, CH_3) ppm.

5.1.24. (3*S*,4*R*)-1-Diazo-3,4-epoxy-tetradecan-2-one 30. To a mixture of (2*R*,3*R*)-epoxy-tridecan-1-ol **29** (8.89 g, 41.5 mmol) in CCl_4 (80 mL), acetonitrile (80 mL) and water (120 mL) was added $NaIO_4$ (29.7 g, 138.8 mmol) and $RuCl_3{\cdot}3H_2O$ (240 mg, 2.2 mol%). The brown mixture was stirred for 2.5 h at room temperature. According to TLC the reaction was complete. Dichloromethane (350 mL) and water (200 mL) were added and the layers were separated. The water layer was extracted with dichloromethane (3×100 mL). After drying ($MgSO_4$) and evaporation of the solvent a black residue was residing. This was dissolved in diethyl ether (500 mL). To the cooled (2 °C) solution was added isobutyl chloroformate (5.66 g, 41.5 mmol), followed by triethylamine (6.26 g, 61.8 mmol). After stirring for 1 h at the indicated temperature the precipitate was filtered off under a stream of nitrogen. The filtrate was added to a solution of diazomethane in diethyl ether (300 mL, concentration of CH_2N_2: 0.3 mmol/mL). After one night at room temperature the reaction mixture was flushed with nitrogen to remove excess diazomethane. Residual $Et_3N{\cdot}HCl$ was filtered off and the solvent was evaporated leaving a black residue. Flash chromatography (EtOAc–hexane 8:1) over silica gel gave the epoxy diazomethyl ketone as a yellow solid (4.93 g, yield calcd on epoxy alcohol 47%), mp 41–42 °C (hexane–diethyl ether). Elemental analysis: calcd for $C_{14}H_{24}N_2O_2$ (252.357): C 66.63, H 9.59, N 11.10%; found: C 66.38, H 9.60, N 10.83%; $[\alpha]_D^{20}$=−65.7 ($CHCl_3$, c=1). IR (CCl_4): ν_{max} 3120 (HC=), 2115 (C=N=N), 1645 (C=O) cm^{-1}. ^1H NMR (300 MHz) ($CDCl_3$): δ 5.41 (1H, s, *H*C=N_2), 3.15 (1H, d, J=1.4 Hz, O–C*H*–C=O), 2.90 (1H, m, $-CH_2CH-O$), 1.6–1.2 [(18H, m, $(CH_2)_9$], 0.81 (3H, t, J=6.9 Hz, CH_3) ppm. ^{13}C NMR: 147.80 *C*=O, 59.26 CH_2C–O, 58.75 O–*C*H–C=O, 51.96 *C*H=N_2, CH_2 signals at 31.85, 31.66, 29.53, 29.45, 29.41, 29.27, 29.21, 25.63, 22.64, CH_3 at 14.08 ppm.

5.1.25. Ethyl (4*R*)-4-acetoxy-tetradec-2-enoate 31. A solution of (3*S*,4*R*)-1-diazo-3,4-epoxy-tetradecan-2-one **30** (2.36 g, 9.35 mmol) in abs ethanol (800 mL) was irradiated for 2.5 h. The reaction was monitored by taking IR spectra. Evaporation of the solvent gave a yellow oil (2.50 g). A mixture of thus obtained ethyl (4*R*)-4-hydroxy-tetradec-2-enoate (5.09 g, 18.7 mmol), pyridine (6.9 g, 85 mmol), acetic anhydride (6.0 g, 60 mmol) and a small amount of DMAP was stirred at room temperature for 18 h. The mixture was poured in ice-water (100 mL) and extracted with ether (3×100 mL). After drying ($MgSO_4$), the solvent was evaporated and the residue was purified by flash chromatography (hexane–EtOAc 20:1), giving **31** as a colorless oil (2.89 g, 50%). IR (CCl_4): ν_{max} 1740 (C=O), 1720 (=C–C=O), 1660 (C=C) cm^{-1}. ^1H NMR (90 MHz) (CCl_4): δ 6.8 (1H, dd, J=15, 4.5 Hz, EtO–C(=O)–CH=C*H*–CH), 5.9 (1H, d, J=15 Hz, O=C–C*H*), 5.5–5.2 (1H, m, C*H*–O–C(C=O)–CH_3), 4.1 (2H, q, J=6.7 Hz, O–CH_2CH_3), 2.0 (3H, s, O=C–CH_3), 1.7–1.1 [(21H, m, $(CH_2)_9$+CH_3CH_2–O)], 0.9 (3H, t, CH_2–CH_3) ppm.

A 400 MHz spectrum was run and the ee was determined (91%) with the aid of the optical shift reagent $Eu(hfc)_3$. The chemical shifts found of the 400 MHz spectrum matched approximately with the 90 MHz spectrum; the values were as follows: 6.84 (1H, d d, J=15.7 Hz, J=5.4 Hz), 5.93 (1H, d, J=15.7 Hz), 4.20 (1H, m), 4.20 (2H, q, J=7.2 Hz), 2.09 (3H, s), 1.33–1.25 (21H, m), 0.88 (3H, t, J=7.2 Hz) ppm.

5.1.26. (5*R*)-5-Decyl-tetrahydrofuran-2-one 32. To a suspension of palladium dichloride (31 mg, 0.17 mmol) in EtOH (15 mL), $NaBH_4$ (15 mg, 0.36 mmol) was added. The mixture was stirred for 15 min and ethyl (4*R*)-4-acetoxy-tetradec-2-enoate **31** (1.08 g, 3.46 mmol) was added. In a closed system the mixture was kept in a hydrogen atmosphere applying a small over-pressure. The theoretical amount of hydrogen was absorbed in 90 min. The mixture was filtered over hyflo and the filtrate was evaporated. The

residue was chromatographed over silica gel (EtOAc–petroleum ether 1:20). Ethyl (4*R*)-4-acetoxy-tetradecanoate was obtained as a colorless solid (827 mg, 76%). IR (CCl_4): ν_{max} 1740, 1730 cm^{-1} (C═O). ^1H NMR (90 MHz): δ 4.85 (1H, m, C*H*–O–C═O), 4.1 (2H, q, *J*=6.7 Hz, CH_3CH_2–O), 2.3 (2H, t, CH_2C(═O)–O), 2.0 (3H, s, O–C(═O)–CH_3), 2.0–1.7 (2H, m, CH_2–CH_2–C(C═O)–OEt), 1.7–1.1 [21H, m, $(CH_2)_9$+O–CH_2–CH_3), 0.9 (3H, t, *J*=6.0 Hz, CH_3-alkyl) ppm.

To a solution of (4*R*)-4-acetoxy-tetradecanoate (980 mg, 3.12 mmol) in EtOH (20 mL) was added KOH (0.8 g, 14.2 mmol). The solution was heated at reflux for 15 min. Then the solvent was evaporated and the residue was dissolved in a small amount of water. After one extraction with ether the aqueous layer was acidified and extracted with ether (3×). These ether extracts were concentrated and the residue was dissolved in benzene (80 mL). A small amount of TsOH was added and the solution was heated at reflux and water was removed azeotropically. The benzene solution was washed with aq. $NaHCO_3$ solution. After drying, evaporation of the solvent gave the product as a pale yellow solid (711 mg, quant.). Recrystallization from heptane gave colorless crystals, mp 35–36 °C, $[\alpha]_D^{20}$=+32 ($CHCl_3$, *c*=1.1), lit.[21] mp 36–37 °C, $[\alpha]_D^{26}$=+29.95 ($CHCl_3$, *c*=2.7). Elemental analysis, calcd for $C_{14}H_{26}O_2$ (226.359): C 74.29, H 11.58%; found: C 74.33, H 11.39%. IR (CCl_4): ν_{max} 1780 (C═O) cm^{-1}. ^1H NMR (300 MHz) ($CDCl_3$): δ 4.5 (1H, m, C*H*OC═O), 2.56–2.50 (2H, m, CH_2C═O), 2.37–2.26 (1H, m, C*H*CH–O–C═O), 1.9–1.26 [19H, m, C*H*CH–O–C═O, $(CH_2)_9$)], 0.88 (3H, t, *J*=6.9 Hz, CH_3) ppm. ^{13}C NMR: 177.25 *C*═O, 81.02 *C*H–O, CH_2 peaks at 35.54, 31.85, 29.53, 29.48, 29.42, 29.30, 29.27, 28.83, 27.97, 25.18, 22.64, CH_3 at 14.07 ppm.

5.1.27. (3*R*/*S*,5*R*)-5-Decyl-3-{[(4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-hydroxy-methyl}-dihydrofuran-2-one 33. To a stirred solution of di-isopropyl amine (505 mg, 5.0 mmol) in THF (10 mL) kept at 0 °C, was added a solution of BuLi in hexane (3.12 mL, 1.6 N). The mixture was cooled at −78 °C and a solution of the lactone **32** (567 mg, 2.5 mmol) in THF (5 mL) was added dropwise, followed by DMPU (390 mg, 2.2 mmol) in THF (5 mL). The solution was stirred for 15 min and (4*S*)-2,2-dimethyl-[1,3]-dioxolane-4-carbaldehyde **38** (1.0 g, 7.7 mmol) in THF (5 mL) was added. The reaction mixture was kept at the low temperature for 4 h and a satd aq. solution of ammonium chloride (25 mL) was added. The organic layer was collected and the water layer was extracted with ether (3×25 mL). After drying over Na_2SO_4, the solvents were evaporated to give a pale yellow oil (730 mg). Chromatography over silica gel (EtOAc–petroleum ether 1:5 gave the product consisting of mainly two isomers (0.56 g, 63%). Some starting material (84 mg, 15%) was also obtained. IR (CCl_4): ν_{max} 3600–3300 (OH, broad), 1760 (C═O), 1380, 1370 (dioxolane absorption) cm^{-1}. ^1H NMR: complex due to the presence of two isomers. This mixture was used as such in the next step.

5.1.28. (5*R*)-5-Decyl-3-[(4*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethylene]-dihydrofuran-2-one 34. To a stirred solution of the isomeric mixture **33** (800 mg, 2.27 mmol) in dichloromethane (20 mL) and pyridine (10 mL) kept at 0 °C a few crystals of DMAP and methanesulfonyl chloride (2.0 mL) were added. After 1 h at room temperature, the dichloromethane was evaporated, the residue was dissolved in ether (30 mL). The solution was washed with water and an aqueous solution of $CuSO_4$. The ether solution was dried over $MgSO_4$ and the solvent was evaporated leaving a yellow oil (825 mg). To a solution of this crude mesylate (825 mg, 1.9 mmol) in dichloromethane (20 mL) DBU (580 mg, 3.8 mmol) was added. The reaction was monitored by TLC. After 2 h the reaction was completed. The dichloromethane solution was washed with aq. bicarbonate and dried ($MgSO_4$). After evaporation of the solvent a mixture of *cis* and *trans* alkene **34** was obtained (620 mg, 96%). IR (CCl_4): ν_{max} 1760 (C═O), 1685 (C═C), 1380, 1370 (dioxolane absorptions) cm^{-1}. This material was then subjected to hydrolysis.

5.1.29. (5*R*)-5-Decyl-3-[(2*R*)-2,3-dihydroxypropylidene]-dihydro-furan-2-one 35. The alkene mixture **34** (560 mg, 1.66 mmol) was dissolved in MeOH (20 mL) and a small amount of TsOH was added. After stirring for 3 h aq. $NaHCO_3$ solution was added and the methanol was evaporated. The residue was treated with water and the mixture was extracted with ether. Usual work-up gave **35** as a colorless solid (380 mg, 77%) which was hydrogenated right away.

5.1.30. (3*S*,5*R*,2′*R*)-5-Decyl-3-(2′,3′-dihydroxy-propyl)-dihydrofuran-2-one, (dihydro rubrenolide) 36. The lactone **35** (380 mg, 1.28 mmol) was dissolved in EtOH (10 mL) and hydrogenated over Pd/C as catalyst at normal pressure at room temperature. After shaking for 3 h in a hydrogen atmosphere the uptake of hydrogen had stopped. Filtration over hyflo and evaporation of the solvent gave a pure residue **36** (320 mg, 84%), mp 105–107 °C (lit.[3] 106–107 °C), $[\alpha]_D^{20}$=+21.8 ($CHCl_3$, *c*=1) (lit.[3] +22, $CHCl_3$). IR and NMR (400 MHz) spectra of **36** were in complete agreement with the spectra obtained from dihydrorubrenolide that was prepared by hydrogenation of authentic rubrynolide obtained from Professor Ollis.[22]

5.1.31. (3*R*/*S*,5*R*)-5-[10-(Tetrahydropyran-2-yloxy)-decyl]-3-{[(4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-hydroxy-methyl}-dihydrofuran-2-one 39. To a solution of di-isopropylamine (450 mg, 4.5 mmol) in THF (20 mL) at 0 °C a solution of BuLi (2.5 mL, 1.6 N) in hexane was added. The stirred solution was cooled to −70 °C and lactone **37** (1.1 g, 3.4 mmol) dissolved in THF (10 mL) was added drop by drop. After stirring for 15 min excess (4*S*)-2,2-dimethyl-[1,3]-dioxolane-4-carbaldehyde **38** (1.17 g, 9.0 mmol) in THF (5 mL) was added in one portion, followed by HMPA (1 mL). The reaction mixture was left for 16 h at −70 °C and was quenched with satd aq. NH_4Cl solution. The mixture was extracted with diethyl ether, the organic phase was washed with water and dried over $MgSO_4$. The residue obtained after work-up was chromatographed over silica gel (100 g, EtOAc–hexane 3:1, followed by 2:1). This gave starting material (0.41 g, 40.8%) and the desired product **39** (400 mg, 26%) as a mixture of isomers which was processed as such in the next step. IR (neat): ν_{max} 3600, 3480 (OH), 2980, 2920, 2840 aliphatic CH_2, 1765 (C═O), 1380,1370 (dioxolane absorptions) cm^{-1}.

5.1.32. (5*R*)-5-[10-(Tetrahydropyran-2-yloxy)-decyl]-3-{[(4*R*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-propylidene}-dihydro-furan-2-one 40. The mixture of alcohols **39** (400 mg, 0.88 mmol) was dissolved in CCl_4 (10 mL) and methanesulfonyl chloride (120 mg, 1.04 mmol) and Et_3N (120 mg, 1.2 mmol) were added. The reaction was followed by IR. The alcohol absorption at 3600 and 3480 cm^{-1} disappeared and strong absorptions at 1380 and 1180 cm^{-1} from the sulfonate were emerging. In addition the C=O absorption shifted to 1775 cm^{-1}. The solution was washed with aqueous bicarbonate solution and dried ($MgSO_4$). After evaporation of the solvent, the crude oily mesylate was immediately used in the next step.

To a solution of the mesylate in diethyl ether (10 mL), DBU (200 mg, 1.33 mmol) was added. The amine·HCl salt formed immediately started to precipitate. According to TLC two products had been formed (*cis* and *trans* alkene **40**). After 2 h the reaction mixture was shaken with 10% aq. tartrate solution and the ether phase was dried over $MgSO_4$. After evaporation of the solvent the residue was chromatographed over silica gel (diethyl ether–hexane 1:1). This gave **40** as an oily mixture of isomers (247 mg, 72.5%) that was used as such in the next step. IR (neat): 1755 (C=O), 1680 (C=C) cm^{-1}.

5.1.33. (5*R*)-5-(10-Hydroxy-decyl)-3-[(2*R*)-2,3-dihydroxy-propylidene]-dihydrofuran-2-one 41. The mixture of *cis* and *trans* alkene **40** was dissolved in MeOH (10 mL), and a small amount of TsOH was added with stirring. The protecting groups were removed fast. The reaction was monitored by TLC. A small amount of aq. bicarbonate solution was added and the mixture was concentrated in vacuo. Water was added to the residue and the mixture was extracted with chloroform (4×). After drying and evaporation of the solvent, triol **41** was obtained as a solid (140 mg, 70%). The solid still showed a long melting point range due to the presence of two isomers. IR (KBr): ν_{max} 3500–3100 (OH), 1750 (C=O), 1680 (C=C) cm^{-1}. This material was used as such in the next step.

5.1.34. (5*R*,3*S*,2′*R*)-5-(10-Hydroxy-decyl)-3-(2′,3′-dihydroxy-propyl)-dihydrofuran-2-one 42. Product **41** was hydrogenated quantitatively in MeOH with H_2 Pd/C to give compound **42** as a solid. IR (KBr): ν_{max} 3500–3200 (OH), 2920, 2840 (aliphatic CH), 1740 (C=O) cm^{-1}. This product was used as such in the next step.

5.1.35. (5*R*,3*S*,4′*R*)-5-(10-Hydroxy-decyl)-3-[(2′,2′-dimethyl-[1′,3′]dioxolan-4′-yl)-methyl])-dihydrofuran-2-one 43. A solution of the above mentioned triol **42** in acetone was stirred with a small amount of TsOH. After 30 min aq. bicarbonate solution was added. The reaction mixture was concentrated and the residue was extracted with ether. After work-up the residue was chromatographed over silica gel (diethyl ether–hexane 1:1). Product **43** was obtained as a solid (115 mg, 73%), mp 78–79 °C (hexane). Elemental analysis, calcd for $C_{20}H_{36}O_5$ (356.477) C: 67.41, H: 10.11%; found: C 67.31, H 9.94%. IR (KBr): ν_{max} 3500–3300 (OH), 1770 (C=O), cm^{-1}. ^1H NMR (400 MHz), ($CDCl_3$): δ 4,35 (1H, m, C*H*–O–C=O), 4.13 (1H, m, CH_2–C*H*–O–CMe_2), 4.07 (1H, m, O–CH–CH*H*–O), 3.64 (2H, t, J=6.6 Hz, CH_2–OH), 3.57 (1H, m, O–CH–C*H*H–O), 2.86 (1H, m, C*H*–C=O), 2.54 (1H, m, C*H*H–CH–C=O, lactone ring), 2.20 (1H, m, C*H*H–CH–C=O, side chain), 1.58 (1H, m, CH*H*–CH–C=O, lactone ring), 1.54–1.20 (25H, m, including dioxolane 2×Me at 1.41 and 1.35) ppm. ^{13}C NMR: 178.62 (*C*=O), 109.20 (O–*C*–O), 79.11 (*C*H–O–C=O), 73.49 (OCH_2–*C*H–O), 69.23 (O–*C*H_2–CH–O), 63.07 (*C*H_2–OH), 38.24 (*C*H_2–C=O), 35.52 (*C*H_2–CH–C=O, lactone ring), 34.20 (*C*H_2–CH–C=O, side chain), 26.96 (C–*C*H_3), 25.65 (C–*C*H_3), other *C*H_2 signals at 35.43, 32.80, 29.50, 29.39, 29.38, 29.30, 25.71, and 25.21 ppm. Another *C*H_2 seems to be hidden at 29.28 ppm.

5.1.36. (5*R*,3*S*,4′*R*)-5-Dec-(9″)-enyl-3-(2′,2′-dimethyl-[1′,3′]dioxolan-4′-yl)-methyl)-dihydrofuran-2-one 44. To a solution of alcohol **43** (69 mg, 0.2 mmol) in dry THF (5 mL) kept under argon, *o*-nitrophenylselanylcyanide (68 mg, 0.3 mmol) was added, followed by tributylphosphine (61 mg, 0.3 mmol) in a small amount of THF. Soon a red colored solution appeared. The mixture was stirred for 2 h at room temperature, after which the starting material had disappeared. After evaporation the residue was chromatographed over silica gel (diethyl ether–hexane 1:1). This gave 98 mg (91%) of the selenide, which was processed further immediately.

To a stirred solution of the selenide in THF (5 mL) an excess of H_2O_2 (0.3 mL, 30%) was added. Stirring was continued for 2 h. TLC pointed out that the reaction was complete. Satd aq. bicarbonate solution was added and the mixture was extracted with hexane. The solution was chromatographed over silica gel. Elution with petroleumether–diethyl ether 1:1 gave a yellowishly colored product **44** (68 mg). Some selenide material was apparently sticking to the product. IR (CCl_4): ν_{max} 2980, 2920, 2855 (aliphatic C–H), 1775 (C=O), 1635 (C=C), and the sharp dioxolane absorptions at 1370 and 1380 cm^{-1}. This product was subjected to hydrolysis right away.

5.1.37. (5*R*,3*S*,2′*R*)-5-Dec-9″-enyl-3-(2′,3′-dihydroxy-propyl)-dihydrofuran-2-one 1 (rubrenolide). Compound **44** (crude 68 mg, 0.2 mmol) was dissolved in MeOH (5 mL). A small amount of TsOH was addded and upon stirring a fast deprotection of the diol function occurred (TLC). Aqueous bicarbonate solution was added and the mixture was concentrated in vacuo. The residue was extracted with ether. The ether solution was dried over $MgSO_4$ and the solvent was removed after filtration. The residue was chromatographed over silica gel. Elution with hexane–EtOAc removed the yellow colored by-product. Elution with EtOAc gave pure compound **1** as a colorless solid (36 mg, 60%), mp 99–100 °C, $[\alpha]_D^{20}$=+21.2 (CH_2Cl_2, c=0.3), lit.[3] mp 100 °C, $[\alpha]_D^{20}$=+21 ($CHCl_3$). The 400 MHz ^1H NMR spectrum was in complete agreement with a 400 MHz NMR spectrum that was taken from the authentic product.

5.2. Separation of rubrenolide 1 and rubrynolide 2

Professor Ollis (University of Sheffield) kindly provided a mixture of the natural product (78 mg) as it was isolated from the natural source; 25 mg of this mixture was dissolved in EtOH (0.5 mL, 95%) and 5% $AgNO_3$ solution in EtOH

(95%, 1 mL) was added. A white precipitate formed immediately. The solid was filtered off and washed with EtOH. The filtrate was concentrated and the residue was treated with water. The mixture was extracted with ether. Drying over $MgSO_4$, filtration and evaporation of the solvent gave rubrenolide (7 mg, mp 98 °C), which was used as reference material. The solid that was filtered off, was treated with a 10% NaCN aq. solution and extracted with ether. After work-up 16 mg of rubrynolide was obtained. This compound was hydrogenated in EtOH with Pd/C as catalyst to give dihydrorubrenolide **36** which was used as reference material (for the 400 MHz spectrum, see preparation of epi-dihydrorubrenolide **28**).

References and notes

1. Franca, N. C.; Gottlieb, O. R.; Coxon, D. T.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1972**, 514.
2. Gottlieb, O. R. *Phytochemistry* **1972**, *11*, 1537. Filho, R. B.; Diaz, P. P.; Gottlieb, O. R. *Phytochemistry* **1980**, *19*(1980), 455.
3. Franca, N. C.; Gottlieb, O. R.; Coxon, D. T. *Phytochemistry* **1977**, *16*, 257.
4. Cahn, S. R.; Ingold, C.; Prelog, V. *Angew. Chem.* **1966**, *78*, 413.
5. Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Fraser Stoddart, J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1480.
6. Taylor, S. K.; Hopkins, J. A.; Spangenberg, K. A.; McMillen, D. W.; Grutzner, J. B. *J. Org. Chem.* **1991**, *56*, 5951.
7. Saito, T.; Thijs, L.; Ettema, G.-J.; Zwanenburg, B. *Tetrahedron Lett.* **1993**, *34*, 3589.
8. For other examples see: (a): Waanders, P. P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett*. **1987**, *28*, 2409. (b) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1495. (c) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1499.
9. Thijs, L.; Dommerholt, F. J.; Leemhuis, F. M. C.; Zwanenburg, B. *Tetrahedron Lett.* **1990**, *31*, 6589.
10. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
11. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
12. Thijs, L.; Waanders, P. P.; Stokkingreef, E. H. M.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 332.
13. Russell, T. W.; Hoy, R. C. *J. Org. Chem.* **1971**, *36*, 2018.
14. Marshall, J. A.; Flynn, G. A. *J. Org. Chem.* **1981**, *44*, 1391. For the preparation of the selenide see: Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
15. Jackson, D. Y. *Synth. Commun.* **1988**, *18*, 337.
16. Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843. See also: Rasmussen, J. R. *J. Org. Chem.* **1980**, *45*, 2725.
17. For a related structure see: Tamamura, H.; Bienfait, B.; Nacro, K.; Lewin, N. E.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **2000**, *43*, 3209.
18. Doolittle, R. E.; Tumlinson, J. H.; Proveaux, A. T.; Heath, R. R. *J. Chem. Ecol.* **1980**, *6*, 473. The assignment *R* and *S* were made opposite to that of the correct structure.
19. An NMR of **31** in the presence of the chiral shift reagent $Eur(hfc)_3$ indicated an ee of 91%.
20. Hubschwerlen, C. *Synthesis* **1986**, 962.
21. Klyne, W.; Scopes, P. M.; Wlliams, A. *J. Chem. Soc.* **1965**, 7237.
22. The late Professor Ollis, kindly provided us with a free sample of the natural product consisting of a mixture of rubrenolide and rubrynolide. The two products could be separated as reported.[3] Rubrynolide was hydrogenated to give dihydrorubrenolide (see Section 5).
23. Horeau, A.; Nouaille, A. *Tetrahedron Lett.* **1971**, 1939.
24. Horeau, A.; Kagan, H. B. *Tetrahedron* **1964**, *20*, 2431.
25. Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
26. Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; Van Derveer, D. *J. Org. Chem.* **1980**, *45*, 3846.
27. Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447, and references cited herein.
28. Minimum energy structures were generated by semi-empirical MOPAC PM3 calculations and carried out by Dr G.J.A. Ariaans (Synthon, Nijmegen, The Netherlands).
29. There are examples of complete control of stereochemistry when both components in the Aldol condensation are chiral, see: Dongala, E. B.; Dull, D. L.; Mioskowski, C.; Solladié, G. *Tetrahedron Lett.* **1973**, 4983. see also: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
30. Girlanda-Junges, C.; Keyling-Bilger, F.; Schmitt, G.; Luu, B. *Tetrahedron* **1998**, *54*, 7735.
31. Ermilova, E. V.; Remizova, L. A.; Favorskaya, I. A.; Tregubova, N. L. *Zh. Org. Khim.* **1975**, *11*, 520.
32. Kang, S. K.; Kim, Y. S.; Lim, J. S.; Kim, K. S.; Kim, S. G. *Tetrahedron Lett.* **1991**, *32*, 363.