Tetrahedron Vol. 44, No. 14, pp. 4371 to 4388, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00
Pergamon Press plc

A FLEXIBLE HYDROAZULENE SYNTHESIS[1]

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(*Received in Germany* 2 *March* 1988)

Abstract - A convergent and stereoselective total synthesis of the hydroazulene system is reported which gives rise to guajanolides (15) and also pseudoguajanolides (27) via the common intermediate 4a.

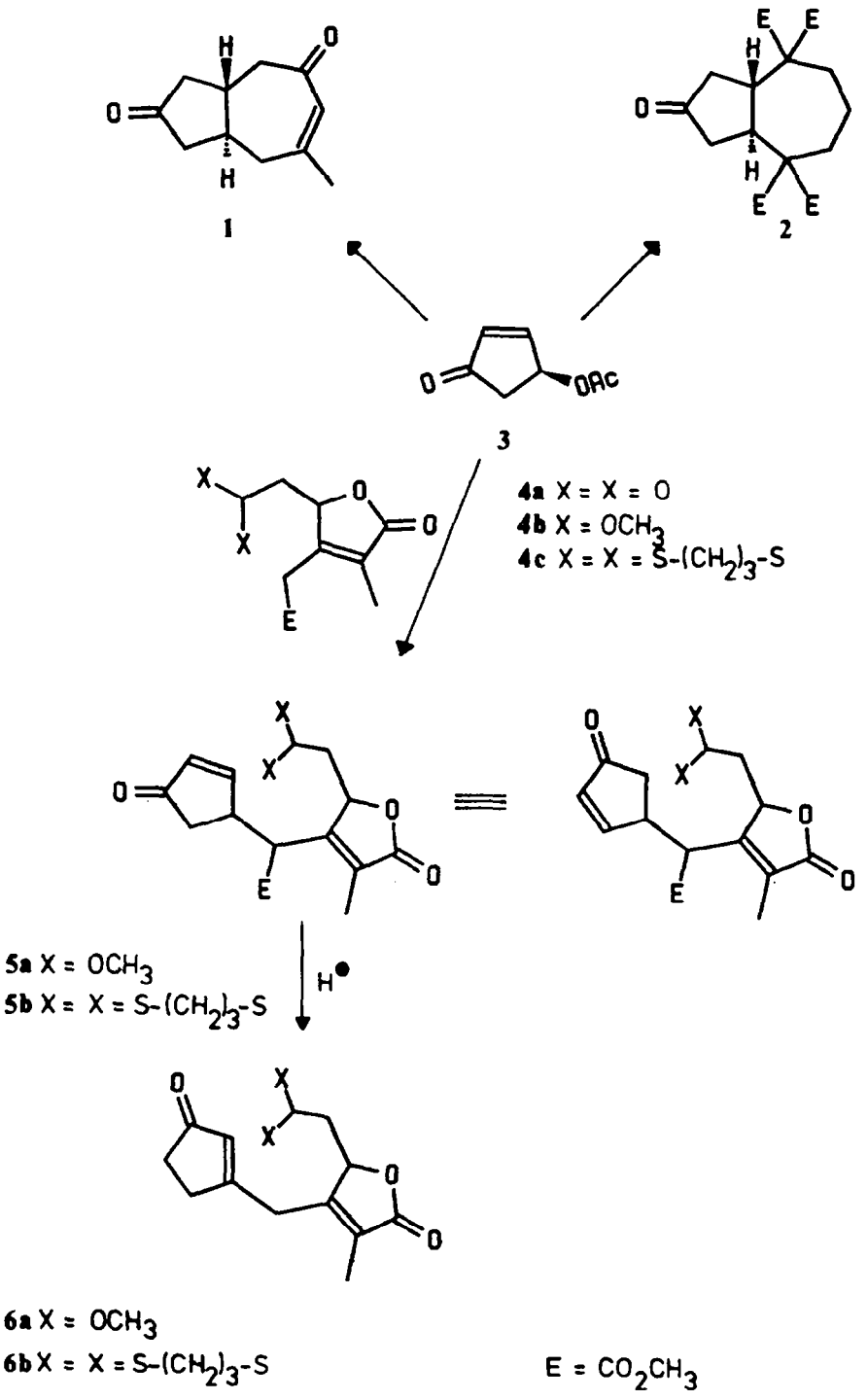
Hydroazulene type sesquiterpene-lactones, owing to their interesting biological activities,[2-11] have been the aim of several synthetic approaches.[12-16] Nearly every retro-synthetic strategy possible has been investigated; the number of enantioselective preparations, however, is still quite small.[17]

As 4-acetoxy-cyclopentenone[18] is easily available as a pure enantiomer and as reliable chirality transfer has been demonstrated for this molecule[19] we investigated various annelation processes with this building block (s. Scheme I).

Early stage double additions to 3 did provide good yields of hydroazulenes 1[20] and 2[21] but both compounds would need various constitutional transformations to give rise to sesquiterpene lactones. Additionally, both products lack constitutional flexibility and in the case of tetraester 2 the symmetric structure of the double donor precludes any application in enantioselective synthesis.

Stimulated however, by the quite simple and highly efficient annelation techniques mentioned above we looked for a non-symmetric building block which, it was hoped, would afford annelation products synthetically very close to natural products and providing high synthetic flexibility. Very promising candidates appeared to be aldehyde 4a or the corresponding acetal 4b, which, following the well established addition-elimination sequence, should provide cyclopentenone 5a - a compound suitable for the substitution of the C-5-methyl group of the guajanolides or any other C-5-substituent by a cuprate addition process. Subsequent aldol cyclization and elimination would introduce the C-7a - C-8 double bond as a stepping-stone for the obligatory C-8-substituent, again to be performed by a 1,4-addition.

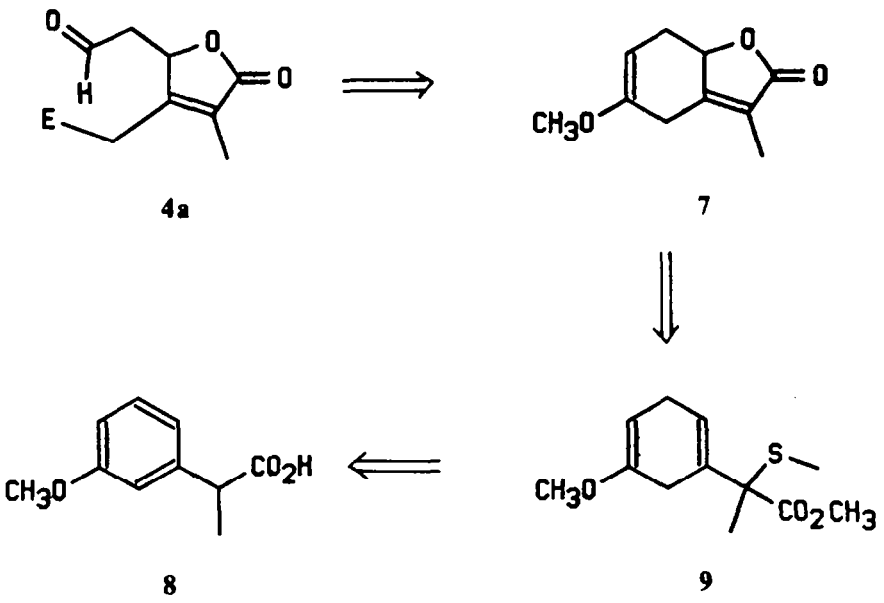
The butenolide moiety of 4b first of all contributes to the C-H acidity at the nucleophilic centre but will later additionally serve as a synthetic equivalent for the lactone group of the various natural products, while the methoxycarbonyl group after having performed its function in the addition process may either just be dismissed by decarboxylation or changed into functionality by oxidative decarboxylation. As either an hydroxy group or a lactone can be found at this position in various natural products, these transformations will keep open all these options.



Scheme I.

Last but not least the well documented proton catalyzed cyclopentenone double bond shift,[22] generating the thermodynamically more stable more highly substituted double bond will provide the unsaturated ketones of type 6, from which cuprate addition should then open the road into the pseudoguajanolide series, similarly leading to all the structural modifications mentioned above.[23]

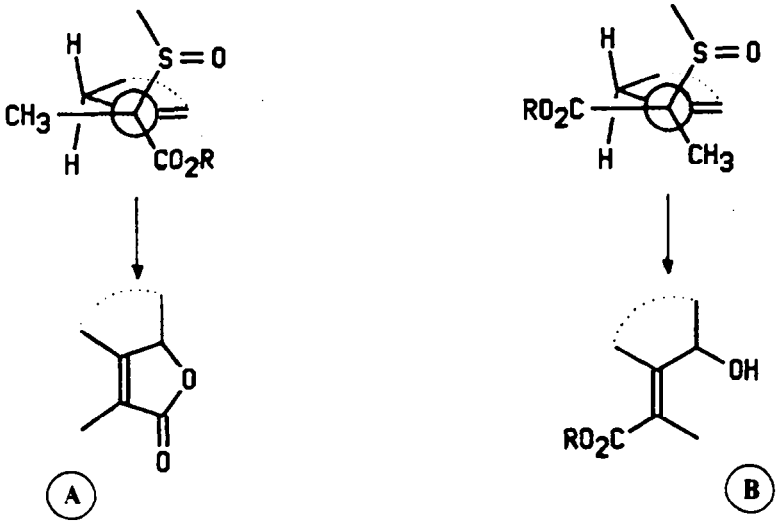
In addition to this high synthetic flexibility, aldehyde 4a and its derivatives should be easily available according to the retro-synthetic reasoning in Scheme II.



Scheme II.

The alkylation product obtained from m-methoxyphenylacetic acid after Birch reduction, diazomethane treatment, and sulfenylation should yield 9, which on subsequent oxidation to the corresponding sulfoxide was expected to undergo a 2,3-sigmatropic rearrangement, followed by a lactonization to form butenolide 7. Selective ozonization should finally yield aldehyde 4a.

All this was borne out by experiment including even one very special detail which had caused some concern. The 2,3-sigmatropic rearrangement of the sulfoxide obtained from 9 could in principle give rise to two different configurations of the exocyclic double bond, only one of them of course being able to form a lactone (Scheme III).

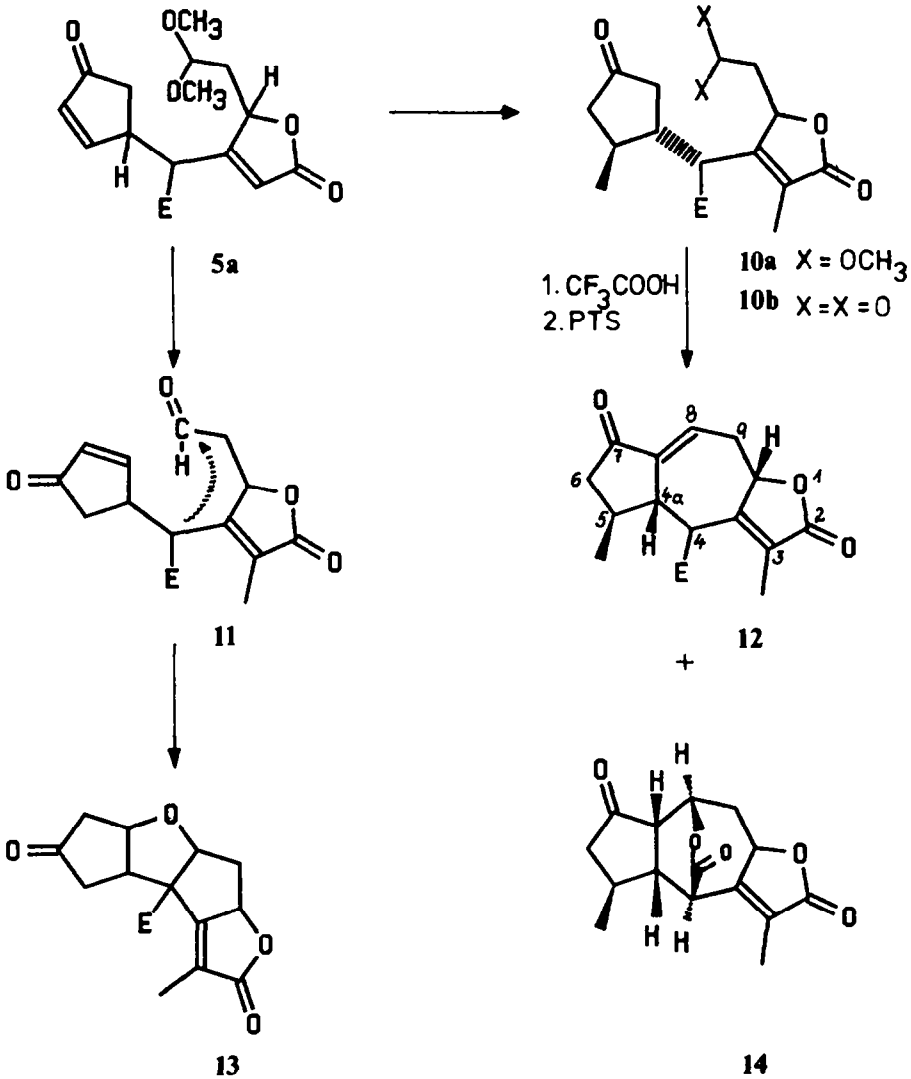


Scheme III.

Predictions were quite uncertain as the outcome should be governed by different energies of transition states (A) and (B) with (A) ending up as the lactone.[24] In the event, without isolation of any intermediates, sulfide 9 was transformed directly into butenolide 7 as by far the main reaction product (60%) thus making this crucial intermediate available in multigramme quantities.

Selective ozonization of 7 proved to be a very efficient process, provided sudan-red was applied to indicate any overreaction and after reduction with dimethyl sulfide, aldehyde 4a as well as the corresponding acetal 4b could be obtained in quantitative yield.

Having a good supply of 4a and 4b the next aim was to find proper conditions for the addition elimination sequence to form cyclopentenone 5a, as a very high substrate specificity of reaction conditions had been noticed in our laboratory for this transformation. 4a and 4b being quite reactive multifunctional molecules, it was not too surprising to find that all the strong bases that had operated satisfactorily with comparatively simple Michael donors gave very disappointing results. Shifting to a solid-liquid phase-transfer process however (toluene, potassium carbonate) and employing 18-crown-6 as a catalyst, changed the situation completely and generated addition product 5a in 90% yield.



Scheme IV.

Cuprate addition to the cyclopentenone moiety proceeded with high trans-selectivity which, however, was proven at a later stage (see Table I) as the resulting diastereomeric esters 10a could be used directly for further transformations. Hydrolysis of the acetal group generated aldehyde 10b in a very clean reaction and subsequent acid catalyzed cyclization of this intermediate led to the desired hydroazulenes (12 and 14) in a combined yield of 57%.

This very clean hydrolysis of the acetal group was also observed with unsaturated ketone 5a prior to the cuprate addition, and as the reaction product 11 looked like a very good candidate for an intramolecular Stetter type cyclization process,[25] it was treated with a thiazolium-salt catalyst and triethylamine. No reaction was observed at room temperature and decomposition occured at higher temperatures. When triethylamine was replaced by diazabicycloundecane (DBU) however, a very quick reaction took place even at 0 °C. The spectral data of the reaction product, which was isolated in 82% yield, immediately ruled out a hydroazulene structure for this compound and were in favour of the interesting tetracyclic ether 13 but without completely establishing the relative configurations. As 13 is obviously formed by aldol cyclization (see arrow in 11) followed by conjugative addition to the cyclopentenone ring the suspicion arose that one was dealing with a simple base catalyzed process without any contribution from the thiazolium salt. Accordingly the reaction was repeated in the absence of this compound and, as expected, 13 was again isolated in high yield. This very efficient cyclization precludes the use of the Stetter route to hydroazulenes and made us concentrate on the aldol cyclization products, which were separated by flash chromatography. The most important observation in connection with these substances is the fact that the main reaction product 12 represents a one to one mixture of epimeric esters at C-4 as was proven by base catalyzed epimerization of both pure epimers. The cis-orientation of the C-5-methyl group to the two protons at C-4a and C-9a was proven by NOE experiments (see Table I).

Table I.

	↯	NOE
12a	4aß	9aß, 4ß, CH_3-5ß
12b	9aß	4aß, 9ß
12b	CH_3-5ß	4aß, 6ß

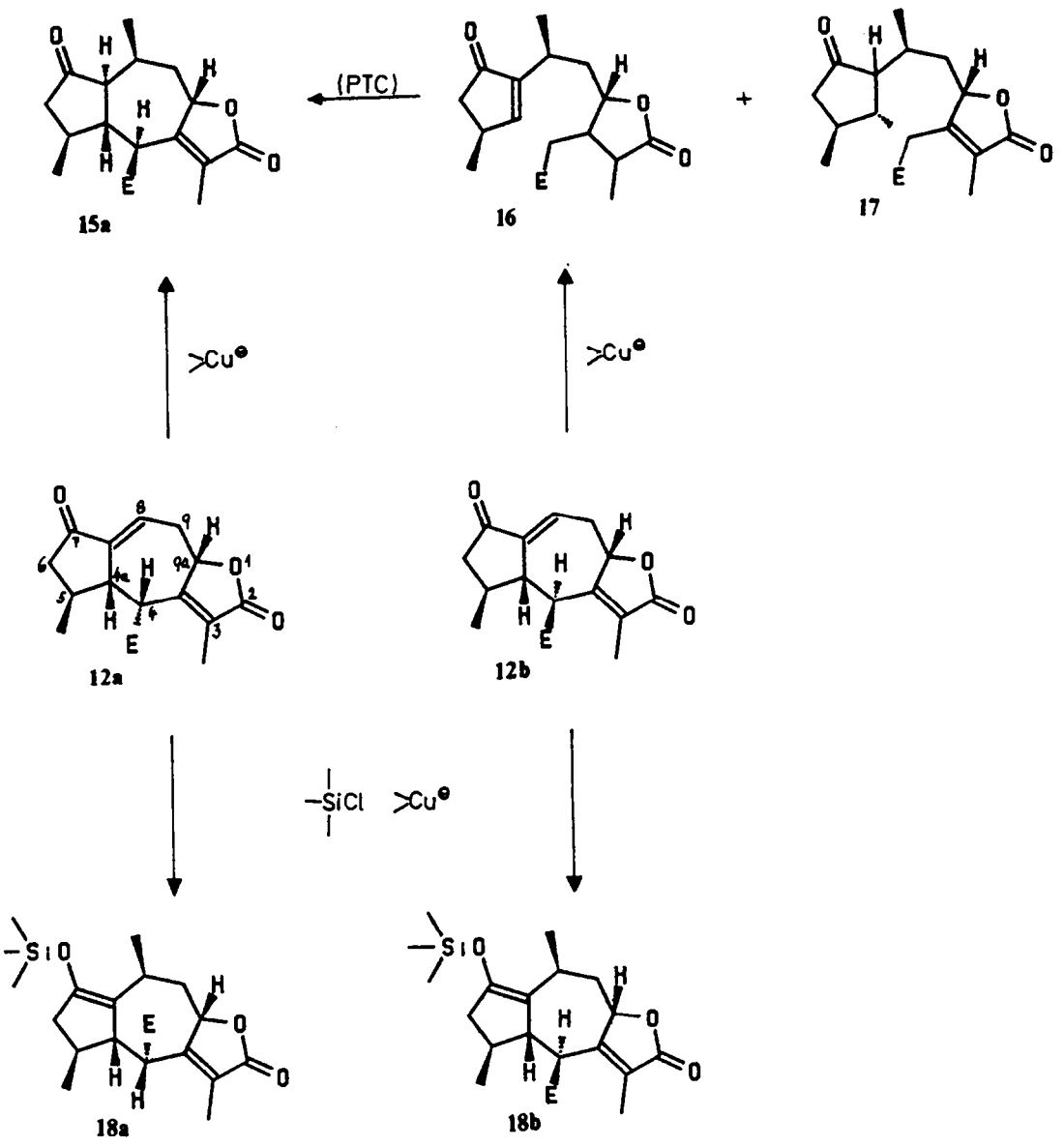
A quite remarkable stability was observed for the minor cyclization product 14 which is obviously formed by lactonisation of the aldol initially formed and in this case represents a 3 : 2 mixture of C-9a epimers. The failure of base catalyzed eliminations to generate enones of type 12 and the high thermal stability of this lactone - slow distillation at 250 °C without decomposition - can be explained by the cis-orientation of the lactone-oxygen and the proton at C-7a (see 14) and this assignment is in line with the 5.5 Hz coupling constant for protons at C-4a and C-4 for both epimeric lactones. This coupling additionally proves both compounds to be C-9a epimers.

As both C-4-epimers 12a and 12b were available by flash chromatography we studied cuprate additions to the C-7a-C-8 double bond separately and although results from simple straightforward conjugate additions were quite poor they did disclose a remarkable configuration dependence of this transformation (see Scheme V). While 12a showed a very high tendency for deprotonation yielding only 25% of the addition product 15a (note C-4-epimerization, probably due to transprotonation processes!) accompanied by C-4-epimers of the starting material, the ß-ester 12b suffered from a fast retro-Michael ring opening triggered by the enolate formed in the cuprate addition. Depending on the amount of cuprate applied, cyclopentenone 16 formed this way may be accompanied by the product 17 from further cuprate addition to the unsaturated ketone.

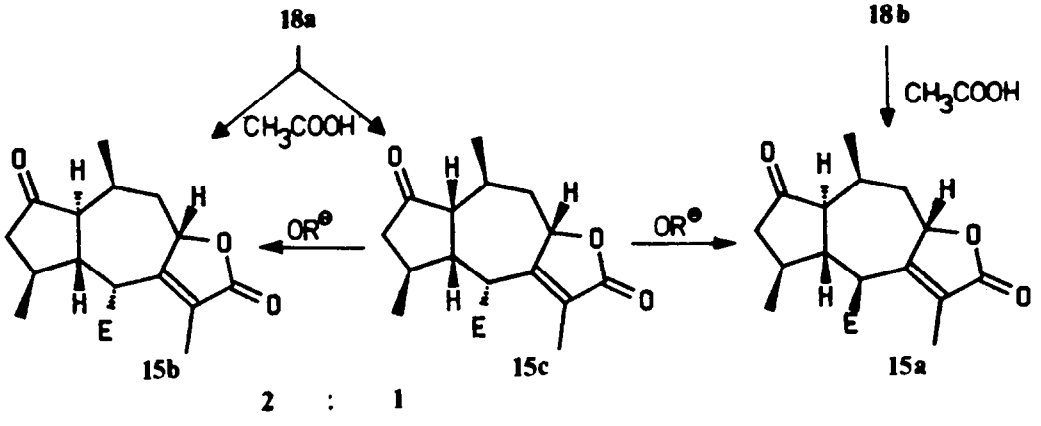
Both unwanted processes, deprotonation as well as retro-Michael decomposition, should be avoided by trimethylsilyl chloride assistance of the addition process. Carbonyl group polarization should enhance nucleophilic attack and capturing of the enolate should block ring opening. Absolutely in line with this reasoning a quantitative yield of enolsilyl ethers 18a and 18b was obtained in a very fast and clean reaction at -78 °C.

These results prove that substituents at C-5 and C-8 can be introduced with high yield, excellent stereoselectivity and also imply high flexibility as many other cuprates can probably be used in this process. Additionally 18a and 18b just differ at the C-4-configuration which of course can be equilibrated under basic conditions. This was checked in connection with the silylenol ether hydrolysis of 18a and 18b. While 18a generated the cis,trans-isomers 15b and 15c in a 2 : 1 ratio, 18b was transformed into 15a exclusively (Scheme VI).

Configuration assignment of these products is of course quite important as these products again should be interconvertible by base-catalyzed equilibration. To leave no doubts about the



Scheme V.



Scheme VI.

configurational relationship between these important guajanolide type products we relied on a combination of chemical results and spectroscopic data together with an X-ray structure analysis to solve this problem. As 15a and 15b showed strong similarities for vicinal coupling constants 15c was first of all epimerized by base treatment to yield a 2 : 1 mixture of 15a and 15b. This experiment proves the 1,5-trans-relationship for both products as an NOE between the protons at C-7a and C-8 was only observed for 15c (see Table II). It is interesting to mention the complete conversion of the cis-annelation product 15c into the corresponding trans-hydroazulenes although generally the cis-configuration in this series proves to be thermodynamically more stable and we assume that the trans-preference in this case is due to the presence of the butenolide ring-system. 15a and 15b were shown to be C-4-epimers by NOE experiments (see Table II), which for both epimers showed a strong NOE between the 8β-methyl group and the protons at C-9a and C-4a thus indicating their cis-relationship. As only 15b showed an NOE between the C-5-β-methyl group and the C-4-proton all these data are in favour of the configurations given in Scheme VI. Completely in line with this assignment both pure esters on treatment with a catalytic amount of sodium methanolate yielded exactly the same 2 : 1 mixture of 15a and 15b, respectively.

Table II.

	↯	NOE
15a	9aβ	9β, 4aβ
15a	CH_3-5β	4aβ, 6β
15a	4α	5α, 7aα
15a	CH_3-8β	9aβ, 4aβ
15b	9aβ	4aβ, 9β, CH_3-8β
15b	CH_3-5β	4β, 4aβ, 6β
15b	4aβ	9aβ, 4β
15b	CH_3-8β	9aβ, 4aβ
15c	4aβ	4β, 9aβ, 7aβ, CH_3-8β

15a being the main material from this sequence we chose this compound for X-ray structure determination. Crystals obtained by recrystallization from a methyl-tert.butyl ether, dichloromethane, petroleum ether mixture have triclinic symmetry, space group P1. The unit cell which has the parameters a=556.94(3), b=999.40(10, c=1495.74(24) pm, α= 98.909(13)°, β=96.817(9)°, γ=96.521(12) contains 2 molecules yielding a calculated density of 1.257 g/cm^3. The data were collected at 293 K on a Syntex $P2_1$ diffractometer using graphite monochromated Cu-K_α radiation (β=154.178 pm) in the θ-2θ mode in the range $3° \leq 2\theta \leq 135$ at a scan speed between 2.93 and 29.30°/min depending on the intensity of the reflection.

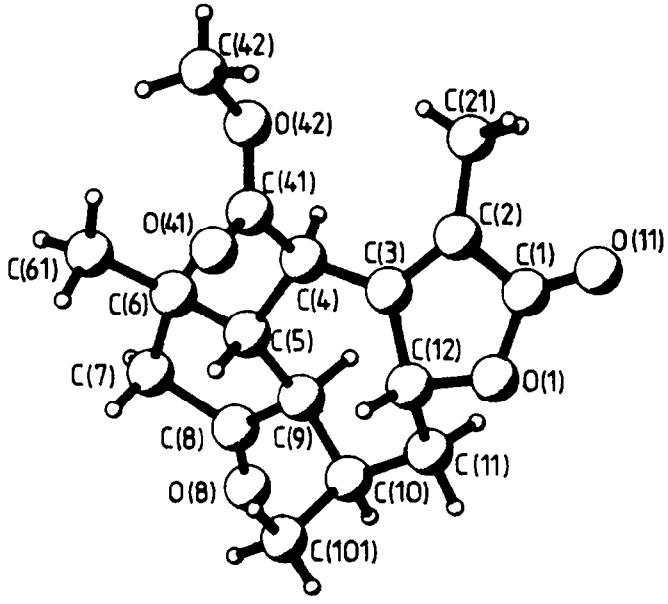


Table III. Positional Parameters and Anisotropic Temperature Factors of 15a

	X/A	Y/B	Z/C	U11	U22	U33	U23	U13	U12
O(1)	-0.1443(2)	-0.3651(1)	0.5093(1)	88(1)	65(1)	43(0)	4(0)	15(0)	6(1)
C(1)	-0.2132(3)	-0.2424(2)	0.4989(1)	70(1)	68(1)	47(1)	13(1)	6(1)	-4(1)
O(11)	-0.2715(3)	-0.2149(2)	0.4243(1)	113(1)	93(1)	47(1)	19(1)	1(1)	2(1)
C(2)	-0.1979(3)	-0.1572(2)	0.5894(1)	56(1)	55(1)	49(1)	12(1)	1(1)	1(1)
C(21)	-0.2524(4)	-0.0139(2)	0.5998(1)	104(1)	65(1)	61(1)	19(1)	-4(1)	21(1)
C(3)	-0.1275(2)	-0.2317(1)	0.6524(1)	43(1)	44(1)	46(1)	7(0)	6(0)	0(0)
C(4)	-0.0717(2)	-0.1804(1)	0.7539(1)	39(1)	35(1)	46(1)	5(0)	4(0)	3(0)
C(41)	0.1728(2)	-0.0903(1)	0.7684(1)	46(1)	38(1)	49(1)	6(0)	4(1)	2(1)
O(41)	0.3631(2)	-0.1327(1)	0.7609(1)	42(1)	56(1)	126(1)	11(1)	15(1)	3(0)
O(42)	0.1500(2)	0.0411(1)	0.7889(1)	61(1)	36(0)	62(1)	2(0)	-1(0)	-1(0)
C(42)	0.3695(3)	0.1369(2)	0.7971(1)	83(1)	46(1)	85(1)	8(1)	-10(1)	-20(1)
C(5)	-0.0651(2)	-0.2903(1)	0.8154(1)	48(1)	36(1)	45(1)	5(0)	4(0)	4(0)
C(6)	-0.0707(3)	-0.2306(1)	0.9171(1)	72(1)	44(1)	43(1)	5(1)	1(1)	3(1)
C(61)	0.1661(4)	-0.1513(2)	0.9693(1)	97(1)	76(1)	54(1)	7(1)	-18(1)	-12(1)
C(7)	-0.1579(4)	-0.3544(2)	0.9578(1)	115(1)	59(1)	50(1)	14(1)	11(1)	-5(1)
C(8)	-0.3162(4)	-0.4500(2)	0.8819(1)	102(1)	49(1)	58(1)	5(1)	30(1)	-9(1)
O(8)	-0.4448(4)	-0.5504(2)	0.8904(1)	197(2)	79(1)	77(1)	-1(1)	56(1)	-65(1)
C(9)	-0.2838(3)	-0.4030(1)	0.7913(1)	58(1)	40(1)	48(1)	3(1)	11(1)	-4(1)
C(10)	-0.2726(3)	-0.5249(1)	0.7162(1)	77(1)	37(1)	54(1)	0(1)	12(1)	-7(1)
C(101)	-0.0540(4)	-0.5989(2)	0.7360(1)	126(2)	49(1)	73(1)	7(1)	20(1)	28(1)
C(11)	-0.2936(3)	-0.4859(2)	0.6213(1)	79(1)	46(1)	49(1)	-3(1)	7(1)	-5(1)
C(12)	-0.1028(3)	-0.3731(1)	0.6061(1)	64(1)	52(1)	43(1)	3(1)	11(1)	6(1)

Table IV. Bond Lengths (pm) and Angles of 15a

C(1)	-O(1)	135.2(2)	C(12)	-O(1)	145.5(2)
O(11)	-C(1)	120.6(2)	C(2)	-C(1)	147.1(2)
C(21)	-C(2)	148.6(2)	C(3)	-C(2)	133.9(2)
C(4)	-C(3)	150.8(2)	C(12)	-C(3)	150.2(2)
C(41)	-C(4)	151.8(2)	C(5)	-C(4)	153.8(2)
O(41)	-C(41)	119.6(2)	O(42)	-C(41)	132.5(2)
C(42)	-O(42)	144.5(2)	C(6)	-C(5)	155.1(2)
C(9)	-C(5)	153.0(2)	C(61)	-C(6)	151.7(2)
C(7)	-C(6)	151.8(2)	C(8)	-C(7)	148.8(2)
O(8)	-C(8)	119.7(2)	C(9)	-C(8)	152.5(2)
C(10)	-C(9)	153.5(2)	C(101)	-C(10)	151.8(3)
C(11)	-C(10)	152.4(2)	C(12)	-C(11)	152.2(2)
H(21)	-C(21)	95(3)	H(22)	-C(21)	90(3)
H(23)	-C(21)	103(4)	H(4)	-C(4)	97(2)
H(421)	-C(42)	91(2)	H(422)	-C(42)	92(3)
H(423)	-C(42)	105(4)	H(5)	-C(5)	102(2)
H(6)	-C(6)	100(2)	H(61)	-C(61)	93(3)
H(62)	-C(61)	94(3)	H(63)	-C(61)	104(3)
H(71)	-C(7)	94(2)	H(72)	-C(7)	90(2)
H(9)	-C(9)	106(2)	H(10)	-C(10)	98(2)
H(101)	-C(101)	109(2)	H(102)	-C(101)	104(3)
H(103)	-C(101)	90(3)	H(111)	-C(11)	103(2)
H(112)	-C(11)	101(2)	H(12)	-C(12)	100(2)

C(12)	-O(1)	-C(1)	109.4(1)	O(11)	-C(1)	-O(1)	121.6(1)
C(2)	-C(1)	-O(1)	109.2(1)	C(2)	-C(1)	-O(11)	129.2(2)
C(21)	-C(2)	-C(1)	121.6(1)	C(3)	-C(2)	-C(1)	107.8(1)
C(3)	-C(2)	-C(21)	130.5(1)	C(4)	-C(2)	-C(2)	125.4(1)
C(12)	-C(3)	-C(2)	109.5(1)	C(12)	-C(3)	-C(4)	125.1(1)
C(41)	-C(4)	-C(3)	105.8(1)	C(5)	-C(4)	-C(3)	116.2(1)
C(5)	-C(4)	-C(41)	110.4(1)	O(41)	-C(41)	-C(4)	124.0(1)
O(42)	-C(41)	-C(4)	112.0(1)	O(42)	-C(41)	-O(41)	124.0(1)
C(42)	-O(42)	-C(41)	116.6(1)	C(6)	-C(5)	-C(4)	112.3(1)
C(9)	-C(5)	-C(4)	113.7(1)	C(9)	-C(5)	-C(6)	104.3(1)
C(61)	-C(6)	-C(5)	116.2(1)	C(7)	-C(6)	-C(5)	103.7(1)
C(7)	-C(6)	-C(61)	112.8(1)	C(8)	-C(7)	-C(6)	105.8(1)
O(8)	-C(8)	-C(7)	125.2(2)	C(9)	-C(8)	-C(7)	109.6(1)
C(9)	-C(8)	-O(8)	125.2(1)	C(8)	-C(9)	-C(5)	104.1(1)
C(10)	-C(9)	-C(5)	118.4(1)	C(10)	-C(9)	-C(8)	111.1(1)
C(101)	-C(10)	-C(9)	112.8(1)	C(11)	-C(10)	-C(9)	112.3(1)
C(11)	-C(10)	-C(101)	112.5(1)	C(12)	-C(11)	-C(10)	116.7(1)
C(3)	-C(12)	-O(1)	103.7(1)	C(11)	-C(12)	-O(1)	106.4(1)
C(11)	-C(12)	-C(3)	115.2(1)				

The data were corrected for Lorentz-, polarization, and absorption effects (μ=0.672 mm^{-1}). The structure was solved by direct methods and difference-Fourier syntheses. Hydrogen positional parameters were determined from difference Fourier maps and refined isotropically. The refinement using 2614 out of 2874 measured independent reflections ($F>4.0\sigma(F)$) converged at R=0.048. A final difference map displayed no electron density higher than 0.22 $*10^6$ e/pm^3. The program SHELX-76[26] and own programs were used. Complex atom scattering factors[27] were employed.[28]

The bonding parameters are all well in the usually observed range. No close intermolecular contacts are found.

As can be judged from these data, this analysis definitely proves the configuration of 15a and, obviously, the conformation of crystalline material is identical with the conformation in solution as all dihedral angles derived from coupling constants fit nicely with this structure determination.

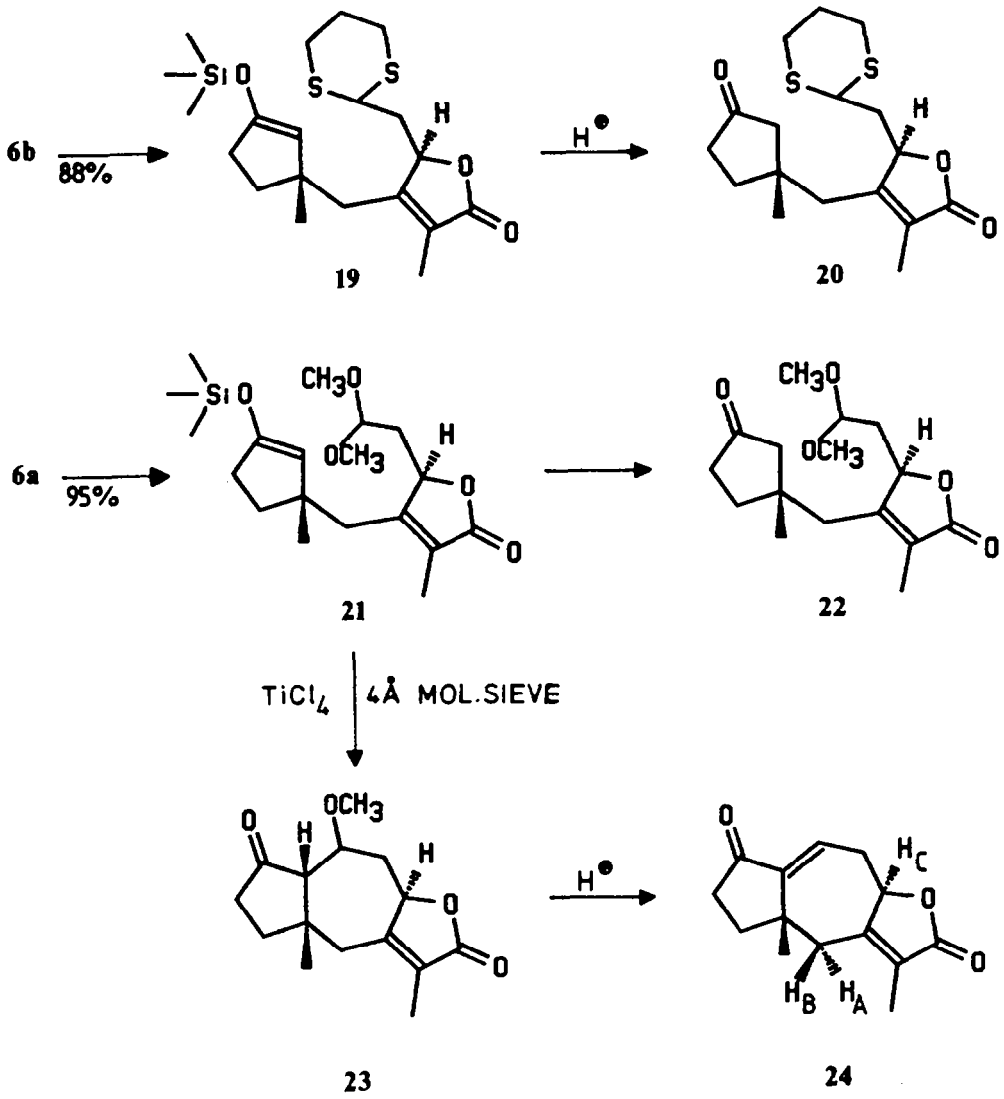
As 15a and 15b represent guajanolide-hydroazulenes and additionally can be interconverted by base-treatment, this pair of epimers, owing to its chemical flexibility, opens the road to various structures of this type.

Prior to pursuing this chemistry, however, we looked into the isomerization of 5 into the thermodynamically more stable cyclopentenone of type 6 and into the cuprate addition to the sterically more hindered double bond of this compound. As the cyclopentenone rearrangement[29] is generally conducted as an acid catalyzed process, we first of all prepared thioacetal 4c as an acid stable building block. After the normal addition elimination sequence it gave rise to cyclopentenone 5b as a mixture of diastereomers. Subsequent treatment with trifluoroacetic acid, however, smoothly converted all the material into cyclopentenone 6b.

Trimethylsilyl chloride capture having been such a big success with unsaturated ketones 12a and 12b, this technique was applied as first choice to 6b, as the formation of quarternary carbon atoms tends to create problems in organometallic reactions. Again this addition proceeded smoothly at low temperature to give a quantitative yield of the enolsilylether 19 (Scheme VII) which, without any further characterization was hydrolyzed giving a 7 : 1 mixture of 20 and its epimer in 94% yield.

The high yield, but particularly the excellent stereoselectivity (88% ds), are the most remarkable observations in connection with this conjugate addition. Obviously, one is dealing with a very efficient 1,4-induction. As long as the ring-open products 19 and 20 were the only ones at hand however, neither the exact relative configuration nor any mechanistic explanation could be forwarded at this stage. The configurations indicated in Scheme VII have actually been deduced from cyclization product 24, which was obtained as follows. As thioacetal 20 and its corresponding aldehyde proved to be poor precursors for the desired cyclization process, 6b was transformed, prior to cuprate addition, into oxygen-acetal 6a by a lead dioxide mediated trans-ketalization. Trimethylsilyl chloride mediated cuprate addition to this compound was as efficient as with thioacetal 6b but unfortunately, its selectivity at -78 °C was somewhat lower (82% diastereoselectivity). Running this addition at -120 °C, however, resulted in a 95% yield of stereoisomer 22 with 95% diastereoselectivity after silyl ether hydrolysis.

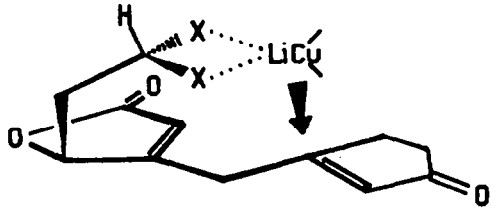
To make use of the very mild and highly efficient Mukaiyama-type cyclization conditions the direct addition product 21 was treated with titaniumtetra chloride in dry dichloromethane in the presence of 4 Å molecular sieves,[30] to give rise to a mixture of the diastereomeric methyl ethers 23 in 93% yield. Subsequent treatment with p-toluene sulfonic acid smoothly generated the unsaturated ketone 24 which appeared an ideal candidate to determine the relative configurations of products in this pseudoguajanolide series. Owing to the quite rigid conformation of this unsaturated ketone, NOE experiments are again the method of choice to solve the problem. As in a 300 MHz ^1H NMR spectrum one can easily differentiate between the 4α-proton H_A and the β-proton H_b and as NOE's are visible between the C-9a-proton H_C and H_A, as well as between H_B and the C-4a-methyl group (see Table V) there is good proof for the trans-orientation of H_C and the C-4a-methyl group as indicated



Scheme VII.

in Scheme VII. Knowing the relative configuration for these cuprate-addition products one is of course tempted to rationalize this result.

One explanation for this remarkably high 1,4-induction could be complex formation between the lithium cuprate and the hetero atoms of the acetal group, which then could direct the reagent into the cyclopentenone double bond from the side of this functionality (see 25).

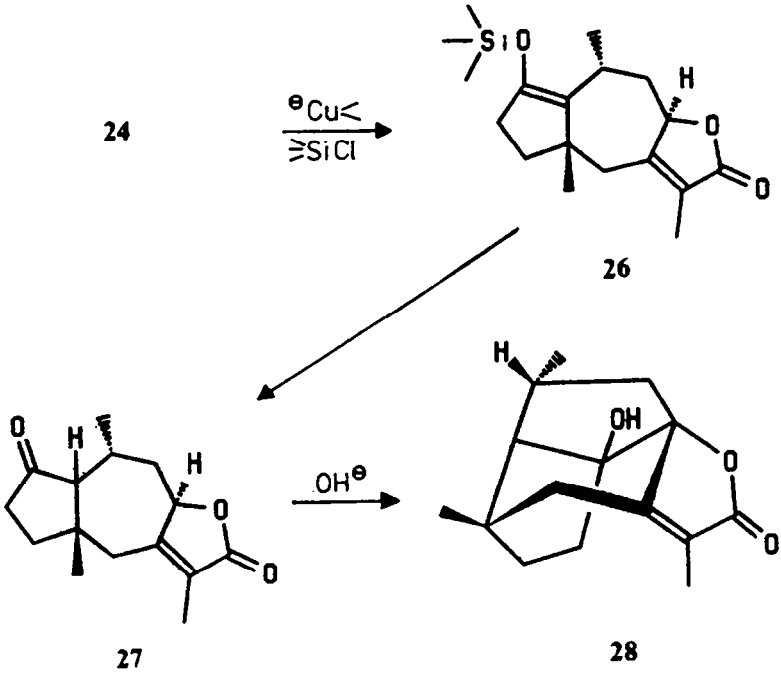


25

Scheme VIII.

If this chelating effect is actually operating the higher selectivity in the case of the more polarizable sulfur groups of the thioketal is easy to understand.

Anyway, these two very efficient transformations - cuprate addition and cyclization - provide a very reliable supply of the pseudoguajanolide system and the last reaction to be investigated was the final cuprate addition to introduce the C-8-methyl group. Operating in the presence of trimethylsilyl chloride again, a very high yield of just one stereoisomer 26 was obtained (see Scheme IX).



Scheme IX.

Table V.

	↯	NOE
24	4β	CH_3-4aβ
24	4α	9aα

Table VI.

	↯	NOE
26	9aα	CH_3-8α, 9α
26	CH_3-8α	9aα, 4α, 8β
26	CH_3-4aβ	4β, 9β, 5β

Its constitution and configuration is clearly indicated by ^1H NMR data including NOE measurements (see Table VI). On hydrolysis a 5 : 1 mixture of C-7a-epimeric ketones 27 was obtained which under equilibrating conditions (treatment with base) underwent a very smooth vinylogue aldol cyclization to generate the tetracyclic compound 28. The fact that both epimers provide this very rigid molecule can be viewed as another proof for the configurational identity at the non equilibrating centres C-4a and C-8.

Obviously, according to expectations no configurational change at these centres is taking place during hydrolysis. There is at the moment no completely reliable argument for exactly defining the C-7a-configuration in the two epimers of ketone 27, but as this centre is located next to a carbonyl group configurational manipulations are possible and experiments are at hand to also solve this problem with an X-ray investigation.

As far as synthetic flexibility is concerned butenolide 4a and its acetal derivatives proved to be quite useful building blocks that open the road into guajanolide as well as pseudoguajanolide sesquiterpenes and additionally give rise to intermediates with the ideal set up for highly stereoselective cuprate additions to introduce substituents at the crucial positions at carbon-atoms C-4a, C-5, and C-8.

EXPERIMENTAL

Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium benzophenone ketyl immediately before use. Dichloromethane was passed through a column of alumina. Trimethylsilyl-chloride was distilled from calcium hydride. All reactions were carried out under an atmosphere of dry nitrogen. Melting points were uncorrected. ^{1}H NMR spectra were taken on the following instruments: Bruker WH 90 (90 MHz), Bruker WP 200 (200 MHz), Bruker AM 300 (300 MHz), and Bruker WM 400 (400 MHz) with tetramethylsilane as internal standard. ^{13}C NMR: Bruker AM 300 (75 MHz) and Bruker WM 400 (100 MHz). IR: Perkin-Elmer 457 and 590. MS: Finnigan MAT 312 (70 eV). C,H Determinations: Heraeus CHN Rapid. Flash chromatography was performed with Baker silica gel (0.03 - 0.06 mm).

2-(3-Methoxyphenyl)-propionic acid (8): To a vigorously stirred solution of 16.6 g (0.1 mol) 3-methoxyphenylacetic acid in 150 ml of THF at -10°C was added 137.5 ml of 1.6 M n-BuLi in hexane (0.22 mol). A white suspension formed that turned homogeneous after the addition of 20 ml (0.11 mol) of hexamethylphosphoricacidtriamide (HMPA). The solution was stirred at room temperature for 30 min and then 7.5 mol (0.12 mol) of MeI was added at 0°C. After stirring at room temperature for 1 h the reaction mixture was neutralized with 10% HCl and extracted with methyl-tert.isobutyl ether (MTB ether). The organic layers were washed with 10% HCl, water, and brine, dried over $MgSO_4$ and the solvent was evaporated to obtain the crude product (18 g, quantitative). IR ($CHCl_3$): 3300 - 2500, 1715, 1603, 1590, 1490 cm^{-1}. ^{1}H NMR ($CDCl_3$, 90 MHz): δ = 10.22 /1/ br s (COOH), 7.30 - 7.14 /1/ m, 6.93 - 6.72 /3/ m, 3.77 /3/ s, 3.69 /1/ q, J = 7.2 Hz, 1.48 /3/ d, J = 7.2 Hz. MS (room temp.): m/z = 180 (M^+, 46) 135 (100), 121 (65), 105 (29), 103 (21). MS (high resolution: Calcd for $C_{10}H_{12}O_3$ 180.0786; Found 180.0785.

Methyl 2-(5-methoxy-1,4-cyclohexadienyl)-2-methylsulfenylpropionate (9): To a stirred suspension of the acid 8 (18 g, 0.1 mol) in liquid ammonia (600 ml), THF (120 ml), and t-butanol (22.2 ml) at -78°C was added lithium (2.8 g, 0.4 mol) in small pieces until a persistent blue color was obtained. Stirring was continued for 1 h at -33°C and after addition of NH_4Cl (21.4 g, 0.4 mol) the ammonia was evaporated with a stream of nitrogen. Water was added and the solution was acidified (pH 4) with 1 M citric acid and extracted with MTB ether. The organic layers were washed with brine, dried ($MgSO_4$) concentrated, and treated with an excess of ethereal diazomethane. Removal of the solvent and purification by flash chromatography (petroleum ether/ether 3 : 1) gave 17.6 g

(M$^+$, 13), 194 (5), 149 (6), 137 (23), 135 (35), 121 (18), 109 (100), 105 (29). MS (high resolution): Calcd for $C_{11}H_{16}O_3$ 196.1099; Found 196.1099.

To a cold (- 10°C) solution of diisopropylamine (5.96 g, 0.059 mol) in 100 ml of THF was added a solution of n-BuLi in hexane (35.6 ml of 1.6 M, 0.058 mol). The reaction mixture was stirred for 20 min and cooled to - 78°C before dropwise addition of a solution of the above ester (10.5 g, 0.054 mol) in THF (25 ml). After 30 min of stirring at - 78°C, the mixture was warmed to - 30°C and dimethyldisulfide (5.2 ml, 0.059 mol) in THF (10 ml) was added. The reaction mixture was allowed to reach room temp., stirred for 1 h and poured into 10% citric acid solution. Extraction with MTB ether, drying of the organic portion, and solvent removal in vacuo afforded the crude sulfide 9 (13 g, 100%). IR ($CHCl_3$): 1730, 1695, 1660, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$, 90 MHz): δ = 5.76 /1/ br s, 4.61 /1/ br s, 3.74 /3/ s, 3.56 /3/ s, 2.99 - 2.66 /4/ m, 1.97 /3/ s, 1.67 /3/ s. MS (room temp.): m/z = 242 (M^+, 3), 208 (21), 181 (12), 162 (23), 149 (100), 135 (49), 121 (34). MS (high resolution): Calcd for $C_{12}H_{18}O_3S$ 242.0977; Found 242.0977.

3a,4,7,7a-Tetrahydro-5-methoxy-3-methylbenzo[b]furan-2(5H)-one (7): To a solution of the above sulfide (13 g, 0.054 mol) in dichloromethane (250 ml) at - 78°C was added dropwise within 1.5 h a solution of 85% m-chloroperbenzoic acid (13.8 g, 0.068 mol) in dichloromethane (200 ml). The mixture was stirred at - 78°C for 1 h and then poured into solution of sodium sulfite and sodium hydrogen carbonate. After extraction with dichloromethane and evaporation of the solvent the remained crude sulfoxide mixture was dissolved in methanol (100 ml) and treated with 25.3 ml (0.21 mol) of trimethylphosphite. The reaction mixture was stirred for 12 h, poured into saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layers were dried and evaporated, and the residue was chromatographed on silica gel (petroleum ether/ether 2 : 1) to give 5.82 g (60%) of 7 as colorless crystals from MTB ether/petroleum ether. m.p. 92 - 93 °C. IR (KBr): 1775, 1698, 1657 cm^{-1}. ^{1}H NMR ($CDCl_3$, 90 MHz): δ = 4.82 /1/ br dd, J = 10 Hz, J = 7 Hz, 3.58 /3/ s, 3.21 /2/ br s, 2.84 /1/ ddd, J = 14.5 Hz, J = 7 Hz, J = 7 Hz, 2.00 /1/ ddddd, J = 14.5 Hz, J = 10 Hz, J = 4 Hz, J = 2 Hz, J = 2 Hz, 1.84 /3/ br s. MS (room temp.): m/z = 180 (M^+, 100), 165 (5), 152 (29), 151 (34), 137 (35), 123 (75), 109 (62). Anal. Calcd for $C_{10}H_{12}O_3$ C, 66.65; H, 6.71; Found C, 66.77; H, 6.66 %.

A second material, eluted from the column with MTB ether was obtained as a colorless oil (0.69 g, 6%) shown to be E-2-(2-hydroxy-5-methoxy-4-cyclohexenylidene)propionic acid methyl ester: IR ($CHCl_3$, 90 MHz): δ = 4.82 /1/ dd, J = 3 Hz, J = 3 Hz, 4.50 /1/ dd, J = 4 Hz, J = 3 Hz, 3.74 /3/ s, 3.54 /3/ s, 3.33 - 3.13 /2/ m, 2.48 - 2.30 /2/ m, 1.96 /3/ dd, J = 2 Hz, J = 1 Hz. MS (room temp.): m/z = 212 (M^+, 34), 194 (79), 181 (27), 180 (21), 162 (44), 152 (100). MS (high resolution): Calcd for $C_{10}H_{16}O_4$ 212.1048; Found 212.1048.

Methyl[3-methyl-5-(2-oxoethyl)furan-2(5H)-on-4-yl]acetate (4a): A 0.1% solution (0.5 ml) of sudan red 7b in methanol was added to a solution of 7 (8.4 g, 0.047 mol) in methanol (300 ml) and dichloromethane (100 ml). Ozonized oxygen was passed at - 78°C through the stirred solution at the rate of 4 g ozone per h until the total discoloration of the dye. Then the reaction vessel was flushed with nitrogen for 20 min at - 78°C and 6.7 ml (0.294 mol) of dimethyl sulfide was added.

The solution was stirred at - 10 °C for 1 h, then at 0 °C for 1 h and finally at room temp. for 1 h. Evaporation of the solvent i.vac. provided 9.96 g (100%) of 4a as a pale yellow oil. IR ($CHCl_3$): 1770 - 1730, 1682 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ = 9.77 /1/ dd, J = 1.5 Hz, J = 1.5 Hz, 5.44 /1/ m, 3.74 /3/ s, 3.43 /2/ ABq, Δν = 23.4 Hz, J = 16.5 Hz, 3.01 /1/ ddd, J = 17.5 Hz, J = 5.5 Hz, J = 1.3 Hz, 2.72 /1/ ddd, J = 17.5 Hz, J = 7 Hz, J = 1.5 Hz, 1.86 /3/ br s. MS (room temp.): m/z = 212 (M^+, 3), 181 (21), 152 (100), 141 (55), 137 (22), 125 (38), 113 (50). MS (high resolution): Calcd for $C_{10}H_{12}O_5$ 212.0685; Found 212.0685.

Methyl[5-(2,2-dimethoxyethyl)-3-methylfuran-2(5H)-on-4-yl]acetate (4b): To the foregoing reaction mixture (containing 9.96 g, 0.047 mol of 4a) was added 16.4 ml (0.141 mol) of trimethylorthoformate and 50 mg of p-toluenesulfonic acid. The solution was stirred at room temp. for 48 h (TLC control!) and the solvent evaporated. The residue after purification by flash chromatography (ether) yielded 10.8 g (90%) of 4b as a colorless oil. IR ($CHCl_3$): 1750, 1675 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ = 5.08 /1/ br d, J = 9 Hz, 4.56 /1/ dd, J = 7 Hz, J = 4 Hz, 3.73 /3/ s, 3.42 /2/ ABq, Δν = 19.8 Hz, J = 16.5 Hz, 3.41 /3/ s, 3.22 /3/ s, 2.18 /1/ ddd, J = 14.2 Hz, J = 7 Hz, J = 3.2 Hz, 1.86 /3/ d, J = 1.2 Hz, 1.67 /1/ ddd, J = 14.2 Hz, J = 9 Hz, J = 4 Hz. MS (room temp.): m/z = 227 (6), 226 (8), 211 (2), 163 (29), 75 (100). Anal. Calcd for $C_{12}H_{18}O_6$ C, 55.81; H, 7.03; Found C, 55.74; H, 7.18 %.

[5-(2,2-Dimethoxyethyl)-3-methylfuran-2(5H)-on-4-yl]-(4-oxo-2-cyclopentenyl)acetic acid methyl ester (5a): To a solution of 10.5 g (40.7 mmol) of 4b and 6.27 g (44.8 mmol) of 4-acetoxycyclopentenone in toluene (800 ml) was added at 0 °C 6.47 g (46.8 mmol) of K_2CO_3 and 0.43 g (4 mol%) of 18-crown-6. The suspension was stirred for 24 h at 0 °C, washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by flash chromatography (ether) furnished 12.4 g (90%) of 5a as a colorless oil. The product consisted of 3 : 1.8 : 1.6 : 1 mixture of stereoisomers as determined by ^1H NMR spectroscopy. Samples of two pure stereoisomers were obtained by careful chromatography on silica gel (ether). IR ($CHCl_3$, mixture of diastereomers): 1755, 1745, 1720, 1670, 1590 cm^{-1}. ^1H NMR: Major diastereomer, m.p. 91.5 - 92.5 °C ($CDCl_3$, 200 MHz): δ = 7.38 /1/ dd, J = 6 Hz, J = 2.2 Hz, 6.31 /1/ dd, J = 6 Hz, J = 2 Hz, 5.02 /1/ ddq, J = 10.5 Hz, J = 2.2 Hz, J = 1.8 Hz, 4.45 /1/ dd, J = 8.5 Hz, J = 3 Hz, 3.74 /3/ s, 3.68 /1/ m, 3.44 /3/ s, 3.44 /1/ d, J = 11 Hz, 3.34 /3/ s, 2.81 /1/ dd, J = 19 Hz, J = 6 Hz, 2.10 /1/ ddd, J = 14 Hz, J = 8.5 Hz, J = 2.2 Hz, 2.04 /1/ dd, J = 19 Hz, J = 2.3 Hz, 1.96 /3/ d, J = 1.8 Hz, 1.49 /1/ ddd, J = 14 Hz, J = 10.5 Hz, J = 3 Hz. Second diastereomer, last fraction, part 1.8 ($CDCl_3$, 90 MHz): δ = 7.63 /1/ dd, J = 5.7 Hz, J = 2.2 Hz, 6.29 /1/ dd, J = 5.7 Hz, J = 2 Hz, 4.87 /1/ dm, J = 10 Hz, 4.64 /1/ dd, J = 8 Hz, J = 3 Hz, 3.76 /3/ s, 3.72 /1/ m, 3.44 /3/ s, 3.37 /3/ s, 3.29 /1/ d, J = 8.5 Hz, 2.50 /1/ dd, J = 18.5 Hz, J = 6.5 Hz, 2.31 /1/ ddd, J = 14 Hz, J = 8.2 Hz, J = 3 Hz, 1.94 /3/ d, J = 2 Hz, 1.91 /1/ dd, J = 18.5 Hz, J = 3 Hz, 1.61 /1/ ddd, J = 14 Hz, J = 10.5 Hz, J = 3 Hz. MS (room temp., mixture of diastereomers): m/z = 307 (2), 306 (3), 275 (2), 247 (3), 205 (6), 161 (16), 75 (100). Anal. Calcd for $C_{17}H_{22}O_7$ C, 60.35; H, 6.56; Found C, 60.37; H, 6.52 %.

[5-(2,2-Dimethoxyethyl)-3-methylfuran-2(5H)-on-4-yl]-(2-methyl-4-oxocyclopentyl)acetic acid methyl ester (10a): To a stirred slurry of cuprous iodide (0.38 g 2 mmol) in 4 ml of ether at - 10°C was added slowly 2 ml of methyllithium solution (2M in ether, 4 mmol) until the suspension became homogeneous and colorless. The resulting 0.33M lithium dimethylcuprate solution was stirred at - 78°C. 5.3 ml (1.78 mmol Me_2CuLi) of this solution was added at - 78°C to 0.5 g (1.48 mmol) of 5a, dissolved in 20 ml THF/ether (1 : 1). The reaction mixture was stirred for 40 min at - 78°C, poured into 5% HCl, and extracted with MTB ether. After washing with saturated sodium sulfite solution and brine the organic layers were dried ($MgSO_4$) and the solvent removed to give 10a (0.52 g, 100%) as an yellow oil. This material was carried on without further purification. The ^1H NMR spectrum of the product indicated it to be an mixture of 4 diastereomers, only two of which could be separated by column chromatography on silica gel (ether). IR ($CHCl_3$, mixture of diastereomers): 1753, 1747, 1674 cm^{-1}. ^1H NMR (90 MHz), first fraction: δ = 5.00 /1/ dm, J = 10 Hz, 4.63 /1/ dd, J = 8 Hz, J = 3 Hz, 3.71 /3/ s, 3.48 /1/ d, J = 10 Hz, 3.45 /3/ s, 3.35 /3/ s, 2.7 - 1.2 /8/ m, 1.96 /3/ d, J = 2 Hz, 1.13 /3/ d, J = 6.5 Hz. Last fraction: δ = 4.89 /1/ dm, J = 10 Hz, 4.65 /1/ dd, J = 8 Hz, J = 3 Hz, 3.73 /3/ s, 3.45 /3/ s, 3.4 - 3.3 /1/ m, 3.38 /3/ s, 2.76 - 1.22 /8/ m, 1.94 /3/ d, J = 2 Hz, 1.07 /3/ d, J = 6.5 Hz. MS (90 °C, mixture of diastereomers): m/z = 352 (M^+, 0.6), 323 (12), 291 (8), 265 (9), 153 (12), 75 (100).

Hydrolysis and Cyclization of 10a: The above crude acetal 10a (0.52 g) was dissolved in 1 ml of trifluoroacetic acid and after addition of a few drops of water stirred at room temp. for 20 min. Upon concentration i.vac. the resulting aldehyde 10b was dissolved in 30 ml of benzene and heated under reflux in a Dean-Stark trap with 10 mg of p-toluenesulfonic acid. After 30 h the solvent was evaporated and the residue chromatographed on silica gel (first petroleum ether/ether 1 : 1, then petroleum ether/ether 1 : 3) to afford 3 fractions:

i) 3a,4,4aα,5,6,7,9,9aß-Octahydro-3,5ß-dimethyl-7-oxoazuleno[6,5-b]-furan-2(5H)-one-4ß-carboxylic acid methyl ester (12b) (86 mg, 20% after recrystallization from MTB ether/petroleum ether). The mother liquor (55 mg, 13%) consisted of approximately equal amount of two other diastereomers of 12a and 12b as determined by ^1H NMR spectroscopy. 12b: m.p. 154 - 156 °C. IR (KBr): 1755, 1734, 1725, 1651 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.72 /1/ ddd, J = 5.1, 4.6, 2.8 Hz, 5.40 /1/ dddq, J = 9.4, 5.6, 1.6, 1.8 Hz, 3.80 /3/ s, 3.77 /1/ ddq, J = 10.5, 1.6, 1.4 Hz, 3.23 /1/ dddd, J = 19.2, 5.6, 5.1, 2.9 Hz, 3.18 /1/ ddddd, J = 10.5, 7.3, 3.4, 2.9, 2.8 Hz, 2.63 /1/ dd, J = 18.3, 7.8 Hz, 2.39 /1/ dddd, J = 19.2, 9.4, 4.6, 3.4 Hz, 2.15 /1/ dddq, J = 9.4, 7.8, 7.3, 6.5 Hz, 2.07 /1/ dd, J = 18.3, 9.4 Hz, 1.80 /3/ dd, J = 1.8, 1.4 Hz, 1.13 /3/ d, J = 6.5 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 202.8 s, 173.0 s, 170.7 s, 157.6 s, 140.0 s, 132.3 d, 126.8 s, 78.1 d, 52.6 q, 50.3 d, 46.3 d, 45.6 tr, 35.6 tr, 33.5 d, 20.7 q, 8.9 ppm q. MS (60 °C): m/z = 290 (M^+, 31) 258 (42), 244 (7), 231 (100), 230 (44), 213 (28), 203 (37), 140 (77). Anal. Calcd for $C_{16}H_{18}O_5$ C, 66.20; H, 6.25; Found C, 65.81; H, 6.22 %.

ii) 3a,4,4aβ,5,6,7,9,9aβ-Octahydro-3,5β-dimethyl-7-oxoazuleno[6,5-b]furan-2(5H)-one-4α-carboxylic acid methyl ester (12a) (97 mg, 23% after recrystallization from MTB ether/petroleum ether). m.p. 181 - 184 °C. IR (KBr): 1757, 1735, 1726, 1675, 1656 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.82 /1/ ddd, J = 6.9, 3.3, 2.4 Hz, 5.19 /1/ ddq, J = 12.2, 4.0, 2.0 Hz, 4.17 /1/ dq, J = 4.0, 0.9 Hz, 3.68 /3/ s, 3.12 /1/ dddd, J = 18.6, 6.9, 4.0, 2.3 Hz, 2.95 /1/ ddddd, J = 10.0, 4.9, 4.0, 3.3, 2.3 Hz, 2.59 /1/ dd, J = 17.6, 7.5 Hz, 2.57 /1/ dddd, J = 18.6, 12.2, 4.9, 2.4 Hz, 2.21 /1/ dddq, J = 12.0, 10.0, 7.5, 6.4 Hz, 2.02 /1/ dd, J = 17.6, 12.0 Hz, 1.87 /3/ dd, J = 2.0, 0.9 Hz, 1.28 /3/ d, J = 6.4 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 202.6 s, 172.9 s, 169.3 s, 158.0 s, 138.7 s, 131.8 d, 126.6 s, 79.0 d, 52.5 q, 47.7 d, 45.6 tr, 44.9 d, 33.7 tr, 32.2 d, 18.6 q, 8.9 ppm q. MS (90 °C): m/z = 290 (M^+, 24) 258 (18), 231 (51), 230 (100), 215 (16), 212 (16), 202 (18), 140 (32). Anal. Calcd for $C_{16}H_{18}O_5$ C, 66.20; H, 6.25; Found C, 65.78; H, 6.44 %.

iii) 3a,4,4aβ,5,6,7,7aβ,8,9,9a-Decahydro-3,5β-dimethyl-8β-hydroxy-7-oxoazuleno[6,5-b]furan-2-(5H)-one-4β-carboxylic acid lactone (14) (57 mg, 14%, a mixture of C-9a epimers in a ratio of 3 : 2, determined by ^1H NMR). A small amount of the pure major epimer was obtained by recrystallization from MTB ether, m.p. (major epimer) 205 - 209 °C (subl.) IR (KBr, mixture of epimers): 1760 - 1740, 1680 cm^{-1}. ^1H NMR ($CDCl_3$/DMSO-d_6, 90 MHz, major epimer): δ = 5.07 /1/ ddd, J = 7.5 Hz, J = 5.5 Hz, J = 1.5 Hz, 4.68 /1/ ddm, J = 10.5 Hz, J = 8 Hz, 4.15 /1/ d, J = 5.5 Hz, 3.60 /1/ br dd, J = 10.5 Hz, J = 7.5 Hz, 3.1 - 2.1 /5/ m, 1.97 /3/ d, J = 2 Hz, 1.83 /1/ ddd, J = 14.5 Hz, J = 10.5 Hz, J = 1.5 Hz, 1.28 /3/ d, J = 6 Hz. Characteristic signals of the second epimer ($CDCl_3$/DMSO-d_6, 90 MHz): δ = 5.20 /1/ dd, J = 8.5 Hz, J = 7.5 Hz, 4.87 /1/ ddm, J = 10 Hz, J = 8 Hz, 4.14 /1/ d, J = 5.5 Hz, 1.93 /3/ d, J = 2 Hz, 1.28 /3/ d, J = 6 Hz. MS (120 °C, mixture of epimers): m/z = 276 (M^+, 25), 258 (19), 232 (28), 230 (25), 204 (31), 198 (60), 97 (100). Anal. Calcd for $C_{15}H_{16}O_5$ C, 65.21; H, 5.84; Found C, 64.90; H, 5.80 %.

[5-(2-Oxoethyl)-3-methylfuran-2(5H)-on-4-yl]-(4-oxo-2-cyclopentenyl)acetic acid methyl ester (11): A solution of 3.0 g (8.9 mmol) of 5a in 8 ml of trifluoroacetic acid was stirred at room temp. for 30 min. Upon concentration i.vac. the residue was dissolved in dichloromethane and the solution was washed with saturated sodium hydrogencarbonate and dried ($MgSO_4$). Removal of the solvent left 2.4 g (93%) of 11 as an oily mixture of diastereomers. This material was carried on without further purification. IR ($CHCl_3$): 1765, 1745, 1720, 1673 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ = 9.79 and 9.72 /1/ each br s, 7.78, 7.76, 7.39 and 7.36 /1/ each dd, J = 5.8 Hz, J = 2 Hz, 6.29 /1/ dd, J = 5.8 Hz, J = 2 Hz, 5.5 - 5.1 /1/ m, 3.78, 3.76 and 3.74 /3/ each s, 3.7 - 1.8 /6/ m, 1.95 - 1.91 /3/ m. MS (room temp.): m/z = 292 (M^+, 6), 274 (5), 263 (8), 233 (31), 215 (18), 211 (18), 161 (38), 81 (100). MS (high resolution): Calcd for $C_{15}H_{16}O_6$ 292.0947; Found 292.0947.

7,13-Dioxo-8-methyl-2,6-dioxatetracyclo[9.3.0.0^{3,10}.0^{5,8}]tetradec-8-ene-10-carboxylic acid methyl ester (13): To a cold (-10 °C) solution of the above ester (1.05 g, 3.6 mmol) in 60 ml of 1,2-dimethoxyethane was added DBU (0.1 ml). After stirring at -10 °C for 30 min the reaction mixture was poured into 2N citric acid solution and extracted with MTB ether. The organic layers were washed with saturated sodium hydrogencarbonate solution and brine, and dried over $MgSO_4$. Removal of the solvent and purification by flash chromatography (MTB ether) yielded 0.86 g (82%) of the tetracyclic ester 13 as a white solid. Spectral data are given for the mixture of diastereomers. IR ($CHCl_3$): 1760, 1745, 1696 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ = 5.5 - 4.5 /3/ m, 3.80 /3/ s, 3.8 - 1.3 /7/ m, 2.22, 2.06 and 1.95 /3/ each d, J = 2 Hz. MS (room temp.): m/z = 292 (M^+, 30), 232 (64), 211 (52), 193 (100), 182 (62), 105 (92). MS (high resolution): Calcd for $C_{15}H_{16}O_6$ 292.0974; Found 292.0974.

Dimethylcuprate addition of 12a: To a cold (-78 °C) solution of 12a (75 mg, 0.26 mmol) in 10 ml of THF was added 1.18 ml of dimethylcuprate solution (0.33M in ether, 0.39 mmol, prepared as described under 10a). The reaction mixture was allowed to warm to -20 °C, stirred at the same temp. for 12 h and poured into 5% HCl. After extraction with MTB ether the organic layers were washed with sodium sulfite solution and brine and dried over MgSO$_4$. The residue was chromatographed

133 - 134.5 °C (for spectral characterization of 15a see the experimental procedure under 15a). Analysis by ^1H NMR of the mother liquor (15 mg) showed an 8 : 1 mixture of 12b : 15a. Fraction 2 contained 32 mg (43%) of recovered 12a.

Dimethylcuprate addition of 12b: To a cold (-78 °C) solution of 12b (40 mg, 0.14 mmol) in 7 ml of THF was added 0.63 ml of dimethylcuprate solution (0.33M in ether, 0.21 mmol, prepared as described under 10a). The reaction mixture was stirred at -20 °C for 1 h and worked up as described above. Chromatography on silica gel (petroleum ether/ether 1 : 1) afforded 16 mg (36%) of [5-[2-(4,5-dimethyl-2-oxocyclopentyl)propyl]-3-methylfuran-2(5H)-on-4-yl]acetic acid methyl ester (17) as a colorless oil (fraction 1) and 18 mg (43%) of [3-methyl-5-[2-(3-methyl-5-oxo-1-cyclopentenyl)-propyl]furan-2(5H)-on-4-yl]acetic acid methyl ester (16) as a colorless oil (fraction 2).

16: IR ($CHCl_3$): 1746, 1700 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.21 /1/ dd, J = 2.5 Hz, J = 1 Hz, 5.06 /1/ dm, J = 9 Hz, 3.73 /3/ s, 3.46 /2/ ABq, Δν = 32 Hz, J = 16.5 Hz, 2.9 - 1.6 /6/ m, 1.84 /3/ br s, 1.21 /3/ d, J = 7 Hz, 1.17 /3/ d, J = 7 Hz. MS (80 °C): m/z = 306 (M^+, 5), 288 (3), 246 (8), 210 (11), 183 (100), 137 (30). MS (high resolution): Calcd for $C_{17}H_{22}O_5$ 306.1467; Found 306.1466.

17: IR ($CHCl_3$): 1755, 1685 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.07 /1/ dm, J = 10.2 Hz, 3.74 /3/ s, 3.44 /2/ ABq, Δν = 38 Hz, J = 16.5 Hz, 2.5 - 2.35 /2/ m, 2.10 /1/ m, 2.0 - 1.6 /4/ m, 1.86 /3/ br s, 1.35 /1/ ddd, J = 14.5 Hz, J = 10.2 Hz, J = 5 Hz, 1.13 /3/ d, J = 5.5 Hz, 1.12 /3/ d, J = 6 Hz, 0.91 /3/ d, J = 7 Hz. MS (room temp.): m/z = 322 (M^+, 7), 304 (3), 231 (11), 210 (96), 183 (100), 139 (26). MS (high resolution): Calcd for $C_{18}H_{26}O_5$ 322.1780; Found 322.1780.

3a,4,4aβ,5,6,7,7aα,8,9,9aβ-Decahydro-3,5β,8β-trimethyl-7-oxoazuleno[6,5-b]furan-2(5H)-one-4α-carboxylic acid methyl ester (15b) and 3a,4,4aβ,5,6,7,7aβ,8,9,9aβ-decahydro-3,5β,8β-trimethyl-7-oxo-azuleno[6,5-b]furan-2(5H)-one-4α-carboxylic acid methyl ester (15c): To a solution of 110 mg (0.38 mmol) of 12a in a mixture of THF and ether (8 ml, 1 : 1) was added trimethylsilyl chloride (0.147 ml, 1.14 mmol). The solution was cooled at -78 °C and treated with 1.52 ml of dimethylcuprate solution (0.5M in ether, 0.76 mmol, prepared as described under 10a). After stirring for 5 min the reaction mixture was poured into 5% HCl and extracted with MTB ether. The organic layers were washed with brine, the solvent was evaporated and the resulting crude silyl enol ether 18a was dissolved in 0.5 ml of acetic acid. After stirring for 30 min at room temp. the reaction mixture was poured into saturated sodium hydrogencarbonate solution and extracted with MTB ether. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated i.vac.. Chromatography on silica gel of the residue afforded 70 mg (60%) of 15b as a white solid and 39 mg (34%) of 15c as a colorless oil (most polar fraction). Recrystallization of 15b from MTB ether/petroleum ether gave colorless crystals: m.p. 197 - 199 °C (subl.).

15b: IR (KBr): 1765, 1743, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.04 /1/ dddq, J = 12.3, 2.5, 1.1, 1.9 Hz, 4.12 /1/ ddq, J = 4.1, 1.1, 1.5 Hz, 3.77 /3/ s, 2.70 /1/ dddq, J = 4.1, 4.0, 3.7, 7.1 Hz, 2.63 /1/ ddd, J = 11.4, 4.1, 1.7 Hz, 2.52 /1/ ddd, J = 17.8, 6.9, 1.7 Hz, 2.26 /1/ ddd, J = 13.4, 3.7, 2.5 Hz, 2.15 /1/ ddd, J = 11.4, 10.7, 4.1 Hz, 1.95 /1/ dddq, J = 12.7, 10.7, 6.9, 6.3 Hz, 1.86 /1/ ddd, J = 13.4, 12.3, 4.0 Hz, 1.77 /1/ ddd, J = 17.8, 12.7 Hz, 1.76 /3/ dd, J = 1.9, 1.5 Hz, 1.28 /3/ d, J = 6.3 Hz, 0.97 /3/ d, J = 7.1 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 216.1 s, 173.2 s, 170.5 s, 159.4 s, 126.4 s, 78.6 d, 55.5 d, 52.4 q, 47.5 tr, 43.9 d, 43.8 d, 38.2 tr, 32.7 d, 28.5 d, 17.7 q, 13.3 q, 8.8 ppm q. MS (60 °C): m/z = 306 (M^+, 34), 288 (4), 274 (12), 247 (16), 246 (30), 183 (56), 170 (58), 137 (100). Anal. Calcd for $C_{17}H_{22}O_5$ C, 66.65; H, 7.24; Found C, 66.24; H, 7.28 %.

15c: IR ($CHCl_3$): 1749, 1677 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.05 /1/ dddq, J = 6.8, 4.8, 0.9, 2.0 Hz, 3.81 /1/ ddq, J = 3.9, 0.9, 0.9 Hz, 3.75 /3/ s, 2.82 /1/ ddd, J = 8.5, 6.7, 3.9 Hz, 2.36 /1/ ddd, J = 18.5, 9.2, 1.5 Hz, 2.29 /1/ dddq, J = 9.2, 5.8, 5.5, 6.7 Hz, 2.25 /1/ ddd, J = 9, 8.5, 1.5 Hz, 2.09 /1/ dddq, J = 9.5, 9, 2-3, 6.5 Hz, 2.04 /1/ ddd, J = 13, 9.5, 6.8 Hz, 1.92 /1/ dd, J = 18.5, 5.5 Hz, 1.86 /1/ ddd, J = 13, 4.8, 2-3 Hz, 1.84 /3/ dd, J = 2.0, 0.9 Hz, 1.19 /3/ d, J = 6.7 Hz, 1.14 /3/ d, J = 6.5 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 215.9 s, 174.1 s, 170.3 s, 155.8 s, 126.3 s, 80.2 d, 57.4 d, 52.3 q, 46.4 d, 45.2 d, 44.9 tr, 38.3 tr, 31.0 d, 27.1 d, 21.7 q, 20.5 q, 10.2 ppm q. MS (60 °C): m/z = 306 (M^+, 14), 288 (12), 274 (21), 246 (34), 210 (28), 183 (22), 137 (27), 86 (73), 84 (100). MS (high resolution): Calcd for $C_{17}H_{22}O_5$ 306.1467; Found 306.1466.

3a,4,4aβ,5,6,7,7aα,8,9,9aβ-Decahydro-3,5β,8β-trimethyl-7-oxoazuleno[6,5-b]furan-2(5H)-one-4β-carboxylic acid methyl ester (15a): A solution of 185 mg (0.64 mmol) of 12b and 0.24 ml (1.92 mmol) of trimethylsilyl chloride in a mixture of THF and ether (8 ml, 1 : 1) was treated at -78 °C with 2.56 ml of dimethylcuprate solution (0.5M in ether, 1.28 mmol). Stirring was continued for 5 min and the reaction mixture worked up as described above. After hydrolysis of the resulting silyl enol ether 18b the crude product was recrystallized from MTB ether/petroleum ether to give 185 mg (95%) of 15a as colorless crystals. m.p. 133 - 134.5 °C. IR (KBr): 1750, 1745, 1735, 1660. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.11 /1/ ddddq, J = 12.0, 3.9, 1.4, 0.6, 1.7 Hz, 3.75 /3/ s, 3.71 /1/ ddq, J = 10.3, 1.4, 0.9 Hz, 2.68 /1/ dddq, J = 4.8, 3.1, 2.8, 0.6, 7.2 Hz, 2.57 /1/ ddd, J = 18.6, 7.5, 1.6 Hz, 2.49 /1/ ddd, J = 11.6, 10.3, 9.8 Hz, 2.42 /1/ ddd, J = 13.3, 3.9, 3.1 Hz, 2.06 /1/ dddq, J = 12.4, 9.8, 7.5, 6.5 Hz, 1.98 /1/ ddd, J = 11.6, 2.8, 1.6 Hz, 1.88 /3/ dd, J = 1.7, 0.9 Hz, 1.83 /1/ dd, J = 18.6, 12.4 Hz, 1.38 /1/ ddd, J = 13.3, 12.0, 4.8 Hz, 1.12 /3/ d, J = 6.5 Hz, 1.00 /3/ d, J = 7.2 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 215.4 s, 172.8 s, 171.2 s, 158.8 s, 127.3 s, 79.1 d, 59.0 d, 52.6 q, 50.2 d, 47.4 tr, 43.0 d, 42.3 tr, 36.6 d, 28.6 d, 18.4 q, 14.3 q, 9.0 ppm q. MS (120 °C): m/z = 306 (M^+, 52) 291 (11), 274 (28), 247 (100), 246 (46), 219 (41). Anal. Calcd for $C_{17}H_{22}O_5$ C, 66.65; H, 7.24; Found C, 66.21; H, 7.34 %.

Base catalyzed isomerization of the pure diastereomers 15a, 15b, or 15c: A solution of 10 mg (0.03 mmol) of 15a (or 15b, or 15c) in 5 ml of methanol was treated with a few drops of sodium methoxide solution (10% in methanol). After stirring for 5 h at room temp. the reaction mixture was diluted with water, acidified with 10% HCl and extracted with MTB ether. The organic layers were washed with saturated sodium hydrogencarbonate and brine and dried ($MgSO_4$). Removal of the solvent left 10 mg (100%) of a white solid, which was shown to be a 2 : 1 mixture of 15a and 15b by ^1H NMR analysis.

Methyl[5-[2-(1,3-dithian-2-yl)ethyl]-3-methylfuran-2(5H)-on-4-yl]acetate (4c): A solution of 2.12 g (10 mmol) of 4a and 1.21 ml (12 mmol) of 1,3-propanethiol in 50 ml of dichloromethane was stirred at room temp. for 1 h. After cooling to -20 °C 0.5 ml of boron trifluoride etherate was added. The mixture was stirred at room temp. for 12 h, poured into saturated sodium hydrogencarbonate solution and extracted with dichloromethane. The organic layers were washed with water, dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by flash chromatography (petroleum ether/MTB ether 1 : 1) to obtain 2.3 g (76%) of 4c as a colorless oil. IR ($CHCl_3$): 1750, 1681 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ = 5.32 /1/ br d, J = 10 Hz, 4.32 /1/ dd, J = 10.7 Hz, J = 3.8 Hz, 3.76 /3/ s, 3.42 /2/ ABq, Δν = 24 Hz, J = 16.5 Hz, 3.0 - 2.8 /4/ m, 2.5 - 1.6 /4/ m, 1.87 /3/ br s. MS (80 °C): m/z = 302 (M^+, 33), 271 (9), 227 (6), 196 (92), 169 (25), 133 (100). MS (high resolution): Calcd for $C_{13}H_{18}O_4S_2$ 302.0646; Found 302.0646.

[5-[2-(1,3-Dithian-2-yl)ethyl]-3-methylfuran-2(5H)-on-4-yl]-(4-oxo-2-cyclopentenyl)acetic acid methyl ester (5b): To a solution of 1.81 g (6 mmol) of 4c and 1.01 g (7.2 mmol) of 4-acetoxycyclopentenone in toluene (150 ml) was added at 0 °C 1.07 g (7.8 mmol) of K_2CO_3 and 0.1 g of 18-crown-6. The resulted suspension was stirred for 24 h at 0 °C, then washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by flash chromatography (ether) furnished 1.94 g (85%) of 5b as a colorless oil. The product consisted of 3.5 : 2.5 : 2 : 1 mixture of diastereomers as determined by ^1H NMR spectroscopy. Spectral data are given for the mixture of diastereomers. IR

($CHCl_3$): 1754, 1737, 1714, 1665 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ = 7.76, 7.63, 7.42 and 7.34 /1/ each dd, J = 5.5 Hz, J = 2 Hz, 6.32 /1/ dd, J = 5.5 Hz, J = 2 Hz, 5.32 and 5.12 /1/ each dm, J = 10 Hz, 4.34 and 4.30 /1/ each dd, J = 11 Hz, J = 3 Hz, 3.81, 3.79, 3.78 and 3.77 /3/ each s, 3.75 - 3.55 /1/ m, 3.43 and 3.32 /1/ each d, J = 12 Hz, 3.0 - 1.5 /10/ m, 1.94 and 1.92 /3/ each d, J = 2 Hz. MS (140 °C): m/z = 382 (M^+, 18), 350 (6), 300 (20), 276 (14), 225 (17), 161 (13), 133 (100). MS (high resolution): Calcd for $C_{18}H_{22}O_5S_2$ 382.0909; Found 382.0908.

5-[2-(1,3-Dithian-2-yl)ethyl]-3-methyl-4-(3-oxo-1-cyclopentenyl)methylfuran-2(5H)-one (6b): A solution of 1.94 g (5.1 mmol) of 5b in 50 ml of 40% trifluoroacetic acid was heated under reflux for 12 h. Upon concentration i.vac. the reaction mixture was diluted with dichloromethane, washed with saturated sodium hydrogencarbonate solution and dried ($MgSO_4$). Removal of the solvent and purification by flash chromatography (MTB ether) furnished 1.2 g (73%) of 6b as an yellow solid. Recrystallization from MTB ether gave yellow crystals: m.p. 111 - 112 °C. IR ($CHCl_3$): 1758, 1713, 1680, 1620 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.95 /1/ ddd, J = 2.8 Hz, J = 1.4 Hz, J = 1.4 Hz, 5.12 /1/ dm, J = 10.3 Hz, 4.33 /1/ dd, J = 11.0 Hz, J = 3.5 Hz, 3.45 /2/ ABq, Δν = 28 Hz, J = 17 Hz, 3.0 - 2.8 /4/ m, 2.62 /2/ m, 2.49 /2/ m, 2.15 /1/ ddd, J = 14.0 Hz, J = 11.0 Hz, J = 2.3 Hz, 2.0 - 1.8 /2/ m, 1.87 /3/ d, J = 1.7 Hz, 1.76 /1/ ddd, J = 14.0 Hz, J = 10.3 Hz, J = 3.5 Hz. MS (120 °C): m/z = 324 (M^+, 23), 216 (100), 192 (17), 188 (38), 187 (37), 174 (32), 150 (47), 117 (91). Anal. Calcd for $C_{16}H_{20}O_3S_2$ C, 59.23; H, 6.16; Found C, 59.09; H, 6.18 %.

5-[2-(1,3-Dithian-2-yl)ethyl]-3-methyl-4-(1-methyl-3-oxocyclopentyl)methylfuran-2(5H)-one (20): To a solution of 1.18 g (3.64 mmol) of 6b and 1.39 ml (10.92 mmol) of trimethylsilyl chloride in a mixture of THF and ether (40 ml, 1 : 1) was added dropwise at -78 °C a cold (-78 °C) solution of dimethylcuprate (21.84 ml, 7.28 mmol, 0.33M in ether, prepared as described under 10a). After stirring for 15 min the reaction mixture was poured into saturated ammonium chloride solution and extracted with MTB ether. The organic layers were washed with brine, the solvent was evaporated and the residue dissolved in 2 ml of acetic acid. After stirring at room temp. for 30 min the reaction mixture was diluted with MTB ether, washed with saturated sodium hydrogencarbonate solution and brine, and dried ($MgSO_4$). Removal of the solvent and purification by flash chromatography (MTB ether) furnished 1.16 g (94%) of a white solid. The ^1H NMR spectrum of the product indicated it to be a 7 : 1 mixture of 20 and its epimer. An analytical sample of 20 was prepared by recrystallization from MTB ether: m.p. 123 - 124 °C. IR (KBr): 1755, 1745, 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.26 /1/ dm, J = 10.8 Hz, 4.38 /1/ dd, J = 11.2 Hz, J = 3.0 Hz, 3.0 - 2.8 /4/ m, 2.76 /1/ d, J = 13.6 Hz, 2.38 /2/ dd, J = 7.7 Hz, J = 7.7 Hz, 2.24 /1/ ddd, J = 14.0 Hz, J = 11.2 Hz, J = 2.0 Hz, 2.24 /1/ d, J = 13.6 Hz, 2.14 /2/ br s, 2.0 - 1.8 /2/ m, 1.91 /2/ dd, J = 7.7 Hz, J = 7.7 Hz, 1.84 /3/ br d, J = 1.1 Hz, 1.71 /1/ ddd, J = 14.0 Hz, J = 10.8 Hz, J = 3.0 Hz, 1.09 /3/ s. MS (120 °C): m/z = 340 (M^+, 31), 265 (3), 234 (16), 133 (100), 119 (40), 97 (48). Anal. Calcd for $C_{17}H_{24}O_3S_2$ C, 59.97; H, 7.10; Found C, 59.94; H, 7.07 %.

5-(2,2-Dimethoxyethyl)-3-methyl-4-(3-oxo-1-cyclopentenyl)methylfuran-2(5H)-one (6a): 2.82 g (8.7 mmol) of 6b, dissolved in 10 ml of methanol and 5 ml of THF was added dropwise at 0 °C to a well stirred suspension of 4.16 g (17.4 mmol) lead dioxide in methanol (8 ml), containing boron trifluoride etherate (3.21 ml, 26.1 mmol) and trimethylorthoformate (0.5 ml). The reaction mixture was allowed to warm to room temp., stirred for 1 h and diluted with dichloromethane (100 ml). The precipitate was filtered and the filtrate was washed with saturated sodium hydrogencarbonate solution and dried ($MgSO_4$). Removal of the solvent and purification by flash chromatography (MTB ether) furnished 2.3 g (93%) of 6a as a white solid. Recrystallization from MTB ether/petroleum ether gave 1.95 g (79%) of white crystals: m.p. 75.5 - 77 °C. IR (KBr): 1745, 1710, 1678, 1620 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.93 /1/ m, 4.92 /1/ ddq, J = 9.8 Hz, J = 3.8 Hz, J = 1.7 Hz, 4.59 /1/ dd, J = 7.6 Hz, J = 3.5 Hz, 3.45 /2/ ABq, Δν = 28 Hz, J = 17 Hz, 3.43 /3/ s, 3.35 /3/ s, 2.62 /2/ m, 2.48 /2/ m, 2.08 /1/ ddd, J = 14.0 Hz, J = 7.6 Hz, J = 3.8 Hz, 1.87 /3/ d, J = 1.7 Hz, 1.63 /1/ ddd, J = 14.0 Hz, J = 9.8 Hz, J = 3.5 Hz. MS (80 °C): m/z = 280 (M^+, 1), 256 (3), 216 (27), 191 (20), 122 (20), 75 (100). Anal. Calcd for $C_{15}H_{20}O_5$ C, 64.27; H, 7.19; Found C, 64.22; H, 7.30 %.

5-(2,2-Dimethoxyethyl)-3-methyl-4-(1-methyl-3-oxocyclopentyl)methylfuran-2(5H)-one (22): Enone 6a (1.93 g, 6.9 mmol) was dissolved in 50 ml of THF and 30 ml of ether and trimethylsilyl chloride (2.62 ml, 20.7 mmol) was added. The solution was treated immediately after cooling to -120 °C (ether - liquid nitrogen bath) with a cold (-78 °C) solution of dimethylcuprate (27.6 ml, 13.8 mmol, 0.5M in ether). The reaction mixture was stirred for 30 min at -120 °C, warmed to -90 °C, poured into a mixture of saturated ammonium chloride and saturated sodium hydrogencarbonate and extracted with MTB ether. The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was dried in a Kugelrohr apparatus (50 °C, 0.05 torr) for 2 h to yield 2.39 g (95%) of the crude silyl enol ether 21 as an yellow oil. This material was used immediately without further purification.

370 mg (1 mmol) of 21 was hydrolyzed with acetic acid as described under 15b, to give after purification by flash chromatography (MTB ether) 282 mg (95%) of the title compound. The ^1H NMR analysis of the product showed a 17.5 : 1 mixture of diastereomers. An analytical sample of the major isomer 22 was prepared by recrystallization from MTB ether/petroleum ether: m.p. 81 - 83 °C. IR (KBr): 1750, 1680 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.03 /1/ ddq, J = 10.3 Hz, J = 2.5 Hz, J = 1 Hz, 4.61 /1/ dd, J = 8 Hz, J = 3 Hz, 3.45 /3/ s, 3.35 /3/ s, 2.74 /1/ d, J = 13.8 Hz, 2.35 /2/ tr, J = 7.7 Hz, 2.27 /1/ d, J = 13.8 Hz, 2.14 /1/ ddd, J = 14 Hz, J = 8 Hz, J = 2.5 Hz, 2.12 /2/ ABq, Δν = 21 Hz, J = 17.1 Hz, 1.88 /2/ tr, J = 7.7 Hz, 1.83 /3/ d, J = 1 Hz, 1.58 /1/ ddd, J = 14 Hz, J = 10.3 Hz, J = 3 Hz, 1.07 /3/ s. MS (60 °C): m/z = 264 (13), 195 (8), 168 (12), 167 (11), 128 (10), 97 (39), 75 (100). Anal. Calcd for $C_{16}H_{24}O_5$ C, 64.84; H, 8.16; Found C, 65.00; H, 8.10 %.

3a,4,4a,5,6,7,9,9aα-Octahydro-3,4aβ-dimethyl-7-oxoazuleno[6,5-b]furan-2(5H)-one (24): To a stirred slurry of powdered 4 Å molecular sieve (2 g, activated by heating at 500 °C i.vac.) and titanium tetrachloride (1.51 ml, 13.8 mmol) in 50 ml of dichloromethane was added at -78 °C a

suspension of the above silyl enol ether 21 (2.39 g) and 1 g of powdered molecular sieve in 30 ml of dichloromethane. After stirring for 30 min at -78 °C the reaction mixture was poured into saturated sodium hydrogencarbonate solution and extracted with MTB ether. The organic layers were washed with brine, dried ($MgSO_4$) and the solvent was evaporated to yield 1.7 g (93%) of 3a,4,4a,5,6,7,7aß,8,9-9aα-decahydro-3,4aß-dimethyl-8-methoxy-7-oxoazuleno[6,5-b]furan-2(5H)-one (23) as an approximately 1 : 1 mixture of C_8 epimers (diastereomers). This mixture could be separated by flash chromatography (MTB/petroleum ether 1 : 1) followed by recrystallization from MTB ether to yield analytical samples of both isomers.

8α-Methoxy isomer (less polar diastereomer): m.p. 115 - 116 °C. IR (KBr): 1759, 1732, 1686 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.91 /1/ ddq, J = 11 Hz, J = 6.6 Hz, J = 1.8 Hz, 4.15 /1/ ddd, J = 6.4 Hz, J = 2.3 Hz, J = 1 Hz, 3.31 /3/ s, 3.06 /1/ ddd, J = 14 Hz, J = 6.6 Hz, J = 6.4 Hz, 2.90 /1/ br d, J = 12.7 Hz, 2.68 /1/ d, J = 12.7 Hz, 2.43 - 2.38 /2/ m, 1.94 /2/ m, 1.88 /3/ dd, J = 1.8 Hz, J = 0.9 Hz, 1.72 /1/ d, J = 2.3 Hz, 1.23 /1/ ddd, J = 14 Hz, J = 11 Hz, J = 1 Hz, 1.14 /3/ s. ^{13}C NMR ($CDCl_3$, 100 MHz): 219.0 s, 174.3 s, 160.8 s, 124.5 s, 80.1 d, 77.6 d, 63.1 d, 57.9 q, 42.0 s, 37.6 tr, 37.3 tr, 37.1 tr, 35.0 tr, 30.0 q, 9.0 ppm q. MS (60 °C): m/z = 264 (M^+, 4), 232 (100), 214 (14), 204 (16), 188 (21), 176 (31), 110 (72). Anal. Calcd for $C_{15}H_{20}O_4$ C, 68.16; H, 7.63; Found C, 68.00; H, 7.59 %.

8ß-Methoxy isomer (most polar diastereomer): m.p. 143 - 145 °C. IR (KBr): 1747, 1735, 1682 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.77 /1/ ddq, J = 6.2 Hz, J = 6 Hz, J = 2 Hz, 3.84 /1/ ddd, J = 8.4 Hz, J = 5.6 Hz, J = 2.1 Hz, 3.33 /3/ s, 2.53 /1/ dd, J = 13.5 Hz, J = 1.6 Hz, 2.44 /1/ dd, J = 5.6 Hz, J = 1.6 Hz, 2.43 /1/ m, 2.32 /1/ ddd, J = 15.4 Hz, J = 8.4 Hz, J = 6 Hz, 2.31 /1/ m, 2.23 /1/ ddd, J = 15.4 Hz, J = 6.2 Hz, J = 2.1 Hz, 2.22 /1/ br d, J = 13.5 Hz, 1.95 - 1.89 /2/ m, 1.85 /3/ dd, J = 2 Hz, J = 0.8 Hz, 1.31 /3/ s. ^{13}C NMR ($CDCl_3$, 100 MHz): 217.1 s, 174.2 s, 158.6 s, 125.1 s, 80.6 d, 76.3 d, 64.4 d, 57.0 q, 43.7 s, 36.8 tr, 35.1 tr, 34.3 tr, 29.9 tr, 28.6 q, 9.2 ppm q. MS (80 °C): m/z = 264 (M^+, 22), 246 (7), 232 (25), 214 (23), 186 (25), 110 (100). Anal. Calcd for $C_{15}H_{20}O_4$ C, 68.16; H, 7.63; Found C, 67.99; H, 7.66 %.

A solution of 1.1 g of the above mixture of diastereomers and 20 mg of p-toluenesulfonic acid in benzene (100 ml) was heated under reflux for 10 h. After cooling to room temp. the reaction mixture was diluted with MTB ether, washed with saturated sodium hydrogencarbonate solution and brine and dried ($MgSO_4$). Removal of the solvent and purification by flash chromatography (MTB ether) afforded 0.88 g (91%) of a white solid, shown by ^1H NMR analysis to be a 17.5 : 1 mixture of 24 and its epimer. Recrystallization from MTB ether/petroleum ether furnished 0.8 g (83%) of the pure diastereomer 24. m.p. 138.5 - 139.5 °C. IR (KBr): 1765, 1731, 1682, 1652 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.76 /1/ dd, J = 9.3 Hz, J = 3.7 Hz, 4.68 /1/ ddq, J = 11.2 Hz, J = 5.1 Hz, J = 1.7 Hz, 3.19 /1/ ddd, J = 15.3 Hz, J = 9.3 Hz, J = 5.1 Hz, 2.93 /1/ d, J = 13.4 Hz, 2.49 /2/ m, 2.33 /1/ dq, J = 13.4 Hz, J = 1.3 Hz, 2.20 /1/ ddd, J = 15.3 Hz, J = 11.2 Hz, J = 3.7 Hz, 2.04 /1/ m, 1.90 /3/ dd, J = 1.7 Hz, J = 1.3 Hz, 1.84 /1/ m, 1.12 /3/ s. ^{13}C NMR ($CDCl_3$, 75 MHz): 204.9 s, 173.5 s, 160.3 s, 148.6 s, 128.2 d, 125.1 s, 79.1 d, 42.0 s, 40.0 tr, 36.1 tr, 35.7 tr, 32.6 tr, 22.8 q, 8.5 ppm q. MS (70 °C): m/z = 232 (M^+, 20), 214 (36), 204 (7), 186 (36), 110 (100). Anal. Calcd for $C_{14}H_{16}O_3$ C, 72.39; H, 6.94; Found C, 72.06; H, 6.93 %.

3a,4,4a,5,6,7,7a,8,9,9aα-Decahydro-7-oxo-3,4aß,8α-trimethylazuleno[6,5-b]furan-2(5H)-one (27): To a solution of 232 mg (1 mmol) of 24 and 0.38 ml (3 mmol) of trimethylsilyl chloride in a mixture of THF and ether (15 ml, 1 : 1) was added dropwise at -100 °C a cold (-78 °C) solution of dimethylcuprate (4 ml, 2 mmol, 0.5M in ether). The reaction mixture was allowed to warm to -78 °C, stirred for 30 min at this temp., poured into a mixture of saturated ammonium chloride and saturated sodium hydrogencarbonate solution and extracted with MTB ether. The organic layers were washed with brine, dried ($MgSO_4$) and the solvent evaporated to yield 310 mg (97%) of the crude silyl enol ether 26 as a single diastereomer. ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.91 /1/ br dd, J = 10 Hz, J = 4.2 Hz, 2.72 /1/ m, 2.62 /1/ d, J = 13.2 Hz, 2.4 - 2.0 /3/ m, 2.26 /1/ d, J = 13.2 Hz, 1.73 /3/ dd, J = 1.6 Hz, J = 1 Hz, 1.7 - 1.6 /3/ m, 1.13 /3/ d, J = 7.3 Hz, 0.86 /3/ s, 0.05 /9/ s.

The crude silyl enol ether obtained above was hydrolyzed by dissolving in acetic acid as described under 15b. Purification by flash chromatography (MTB ether) afforded 225 mg (91%) of 27. The product was a 5 : 1 mixture of epimers at C_{7a} as determined by ^1H NMR spectroscopy. A small amount of the pure major epimer was obtained by several recrystallizations from MTB ether/petroleum ether : m.p. 150 - 151 °C. IR (KBr): 1742, 1672 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.88 /1/ ddq, J = 7.2 Hz, J = 2.1 Hz, J = 2.0 Hz, 2.51 /1/ dd, J = 13.2 Hz, J = 1.6 Hz, 2.4 - 2.3 /3/ m, 2.26 /1/ br d, J = 13.2 Hz, 1.93 /2/ m, 1.87 /3/ d, J = 2.0 Hz, 1.85 /2/ m, 1.80 /1/ m, 1.19 /3/ d, J = 7.4 Hz, 1.19 /3/ s. ^{13}C NMR ($CDCl_3$, 75 MHz): 218.0 s, 174.6 s, 159.1 s, 125.8 s, 82.1 d, 65.1 d, 44.4 s, 35.8 tr, 35.6 tr, 34.4 tr, 32.5 tr, 27.5 q, 25.8 d, 21.4 q, 9.6 ppm q. MS (80 °C): m/z = 248 (M^+, 24), 230 (6), 219 (9), 215 (5), 151 (44), 124 (24), 97 (100). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.56; H, 8.12; Found: C, 72.49; H, 8.12 %.

The minor epimer has the following ^1H NMR spectrum ($CDCl_3$, 200 MHz): δ = 4.86 /1/ br d, J = 11.5 Hz, 3.06 /1/ d, J = 14.8 Hz, 2.4 - 1.7 /9/ m, 1.85 /3/ dd, J = 1.5 Hz, J = 1.5 Hz, 1.28 /3/ d, J = 6.5 Hz, 0.91 /3/ s.

(1RS,2RS,4RS,10SR,13RS)-13-Hydroxy-6-oxo-2,7,10-trimethyl-5-oxa-tetracyclo[8.3.0.$0^{4,8}$.$0^{4,13}$]tridec-7-ene (28); Attempted base catalyzed equilibration of the mixture of epimers 27: 10 mg (0.04 mmol) of 27 (5 : 1 mixture of C_{7a} epimers) was dissolved in methanol (5 ml) and 1 drop of sodium methoxide solution (10% in methanol) was added. After stirring for 1 h at room temp. the reaction mixture was diluted with water, acidified with 10% HCl and extracted with MTB ether. The organic layers were washed with saturated sodium hydrogencarbonate solution and brine and dried ($MgSO_4$). Removal of the solvent left 10 mg (100%) of 28 as a white solid.

Recrystallization from MTB/ether gave colorless crystals: m.p. 141 - 142 °C. IR ($CHCl_3$): 3600 - 3300, 3590, 1755, 1691 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.35 /1/ br s, 2.3 - 2.2 /2/ m, 2.06 /1/ ddq, J = 7 Hz, J = 7 Hz, J = 7.1 Hz, 1.88 /1/ dd, J = 12 Hz, J = 8 Hz, 1.85 /1/ br s, 1.78 /3/ br d, J = 1 Hz, 1.73 /1/ ddd, J = 12 Hz, J = 7 Hz, J = 2 Hz, 1.6 - 1.3 /4/ m, 1.23 /3/ d, J = 7.1 Hz, 1.07 /3/ s. MS (40 °C): 248 (M^+, 66), 230 (10), 215 (10), 152 (99), 107 (54), 97 (100). Anal. Calcd for $C_{15}H_{20}O_3$ C, 72.56; H, 8.12; Found C, 72.53; H, 8.16 %.

Acknowledgement - These investigations were constantly supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie and this help ist gratefully acknowledged. Orlin Petrov is very thankful to Anton Kalojanoff Foundation, München, and Friedrich Ebert Foundation, Bonn, for fellowships.

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