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Pure Enantiomers from Retro-Diels-Alder Processes

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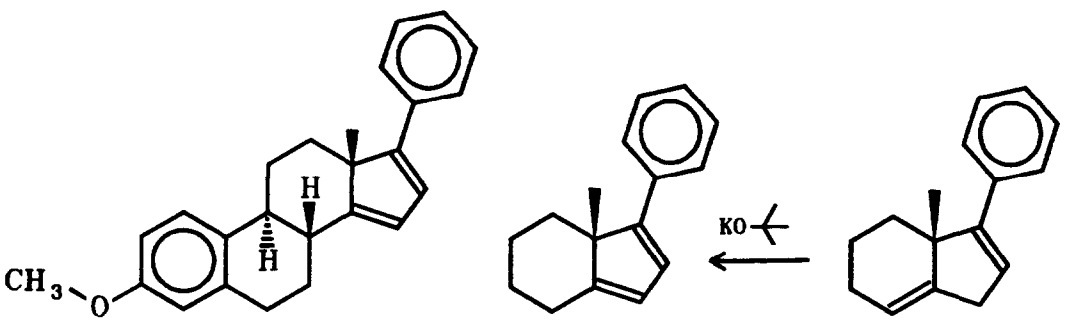
Abstract Diastereoselective and regioselective transformations of cycloadducts to enantiomerically pure cyclopentadienes are reported Retro-Diels-Alder processes finally give rise to pure enantiomers in high yield

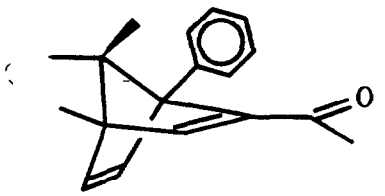
We recently[1] reported on the preparation of the optical active cyclopentadienes **1** and **2** and their use as chiral templates.

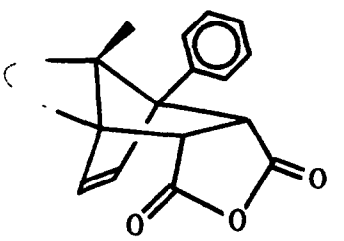


1 **2** **3**

As the preparation of the hydrindane derivative **2** presents the opportunity to in principle generate both enantiomers and in contrast to steroid derivatives opens the road to the R-series as well as the S-series of chiral compounds we were very interested in a high yield and absolutely reliable route to diene **2**. This has in the meantime been achieved by changing the conditions for the isomerization of the easy to make deconjugated diene **3**, described earlier.[1] While the first reported isomerization with multigram quantities gave sometimes unacceptable low yields, the new technique employing potassium tert.butylate in DMSO at room temperature gives consistently high yields and represents a substantial improvement of this procedure

Both dienes **1** and **2** gave with butinone and maleic anhydride quantitative yields of cycloadducts of type **4** and **5** in a high pressure Diels-Alder cycloaddition at 6 - 7kbar.[1]



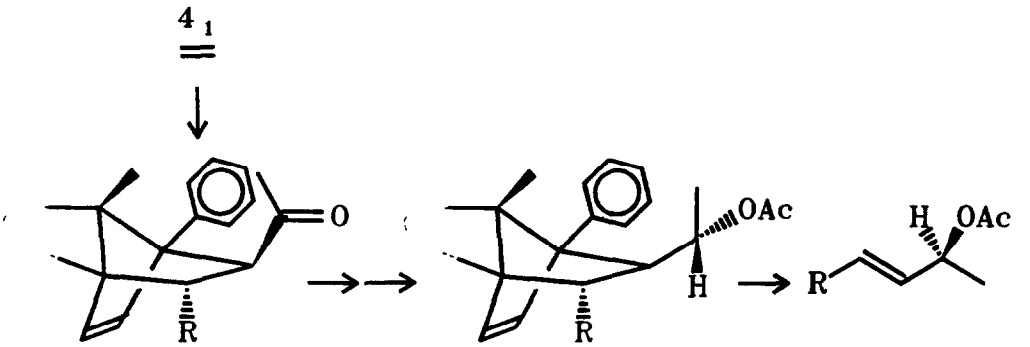


$\underline{\underline{4_1}}$ (FROM 1) $\underline{\underline{5_1}}$

$\underline{\underline{4_2}}$ (FROM 2) $\underline{\underline{5_2}}$

A large number of other dienophiles have been added in a highly stereoselective and regioselective manner too and these results will be communicated in a forthcoming paper.

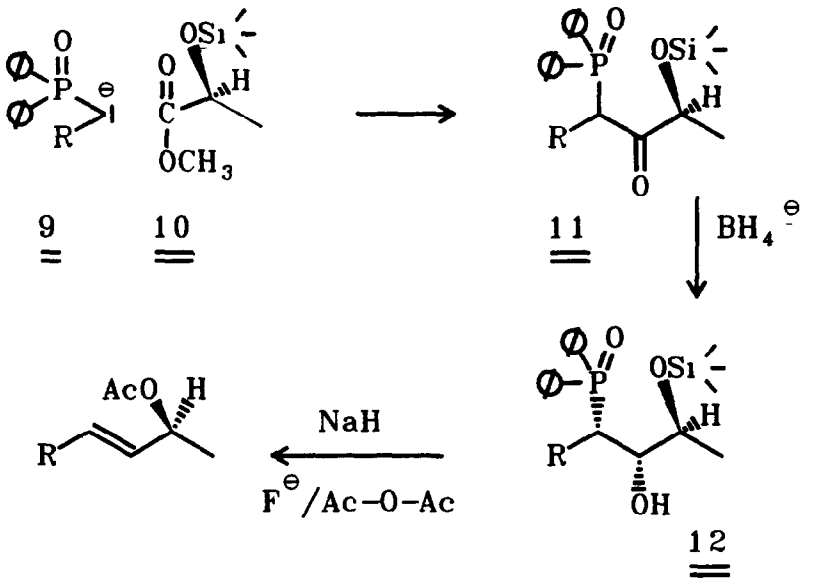
Unsaturated ketones of type **4**, serve extremely well for the preparation of enantiomerically pure allylic alcohols or their corresponding acetates **8** if they are treated with cuprates (**6**) followed by selectride reduction, acetylation (**7**) and a subsequent thermal Retro-Diels-Alder reaction at about 200°C.

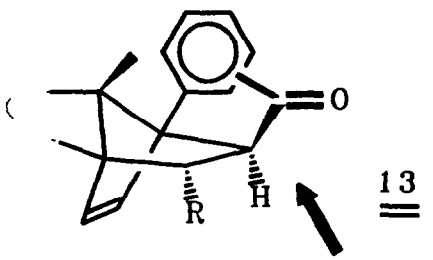


$\underline{\underline{6a}}$ R=CH_3 $\underline{\underline{7a}}$ $\underline{\underline{8a}}$

$\underline{\underline{6b}}$ R=C_4H_9 $\underline{\underline{7b}}$ $\underline{\underline{8b}}$

The retro reaction was simply conducted in a Kugelrohr apparatus and gave a 90% yield of the acetates **8a** and **8b**. The optical purity of these compounds was secured by NMR-shift measurements within benzene and proved to be higher than 98% ee. The absolute configuration was determined by comparing the Retro-Diels-Alder products to the acetates of allylic alcohols prepared from the silyl ether of methyl S-lactate **10** by S.Warren's[2] procedure employing phosphinoxide **9** via condensation product **11** and its borohydride reduction product **12**.

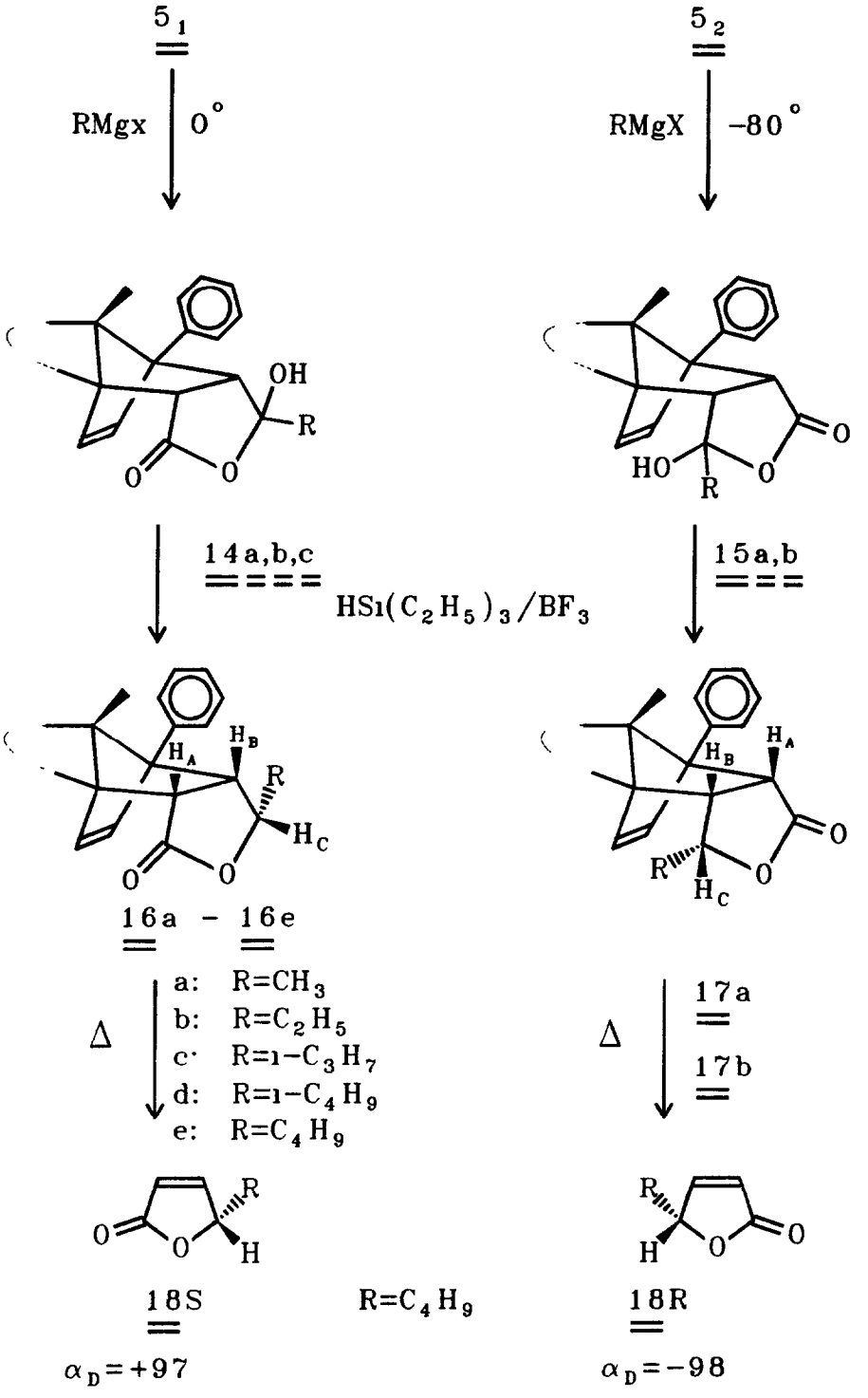




The high stereoselectivity of the selectride reduction is explained by transition state **13**. The backside of the carbonyl group being shielded by the phenyl group,which according to our earlier X-ray investigations[1] is orientated perpendicular to the steroid backbone, exclusive front-side attack of the hydride donating species is secured. High stereoselectivity and interestingly also excellent regioselectivity was observed with the anhydride adducts of type **5**, too In this case additionally a most useful and quite interesting change in regioselectivity was noticed in changing from adduct 5_1 to the hydrindane derivative 5_2.

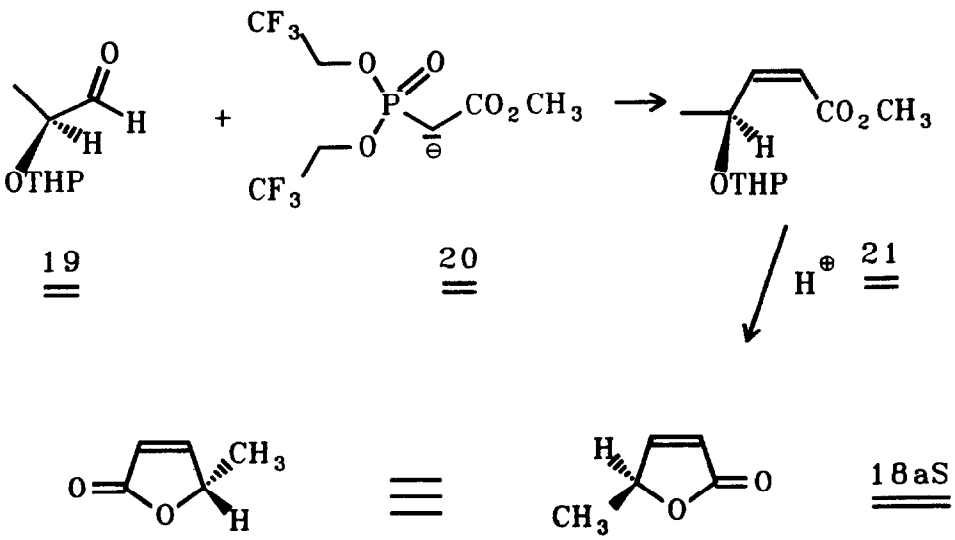
While 5_1 on treatment with Grignard reagents at 0°C yielded after reduction with triethylsilane and trifluoroacetic acid lactones of type **16**, the same reaction sequence afforded a 1:1 mixture of the regioisomers **16** and **17** (NMR data!) in the hydrindane series (5_2). If, however, these Grignard reactions were run at -80°C the regioisomer **17** turned out to be the major reaction product (6 . 1) after silane reduction.

Additionally special care had to be taken in both cases with the methyl Grignard reagent though, as with this nucleophile a very high tendency to form geminal dimethyl groups was noticed. The formation of this useless byproduct could be completely avoided, however, by changing to the corresponding

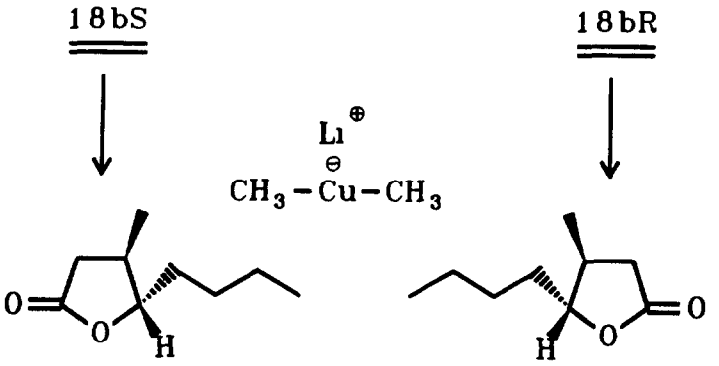

5 1
RMgx
0°
5 2
RMgX
-80°
OH
R
O
O
HO
R
O
O
14a,b,c
HSi(C2H5)3/BF3
15a,b
HA
HB
R
HC
O
O
HB
HA
R
HC
O
O
16a - 16e
a: R=CH3
b: R=C2H5
c: R=i-C3H7
d: R=i-C4H9
e: R=C4H9
Δ
Δ
17a
17b
R
O
O
H
R
H
O
O
18S
R=C4H9
18R
αD=+97
αD=-98

trimethylsilylmethylbromide which operates as the bulky substitute of the methyl Grignard reagent. Double attack does not take place any more and the silyl group is in the subsequent reduction step completely removed by protodesilylation. Although chemoselectivity is achieved this way the hydrindane derivate 5_2 again gave rise to a 6.1 mixture of regioisomers with compounds of type 17 again prevailing strongly

The first indication for this change in regioselectivity resulted from the NMR data of **16** and **17**. While H_A and H_B resonated at δ = 3.50 and δ = 4.05, respectively with compounds of type **16** (R = CH_3) the corresponding signals in product **17** (R = CH_3) of the hydrindane series were registered at δ = 4.14 and δ = 2.98. The relative cis-configuration for H_B and H_C, resulting of course from a highly selective exo-attack of the silane was firmly established by their 8 Hz coupling constant in both types of compounds. To prove that the quite different δ-values for H_A and H_B are not due to the different ring structure of the hydrindane derivatives we generated the corresponding butenolides **18** in a thermal Retro-Diels-Alder reaction, which provided the optical active, unsaturated lactones in a quantitative yield and higher than 98% enantiomeric excess and were pleased to note that both antipodes were obtained from the different series. Although the optical rotation values[3] (see formula **18**) indicated already the S-configuration for products from the steroid series and the R-configuration for butenolides resulting from 5_2 - as could be expected from the constitutions and configurations given for their precursors **16** and **17** - we additionally proved the absolute configuration of one set of butenolides in the case of angelica lactone (R = CH_3) by an independent synthesis from S-methyl lactate. The correct configuration assignment was of course considered crucial with these butenolides as it represents the final proof for the direction of the change in regioselectivity for both series of anhydrides The highly Z-selective Horner-Emmons reaction using Clark Still's phosphonate[4] **20**, afforded a high yield of the THP-protected unsaturated hydroxyester **21** which on mild acid treatment was cleanly transformed into the S-butenolide corresponding to the steroid series thus leaving no doubt for the configuration assignments given in **16** and **17**



Having these butenolides available we made for the case R = C_4H_9 sure that also the trans disubstituted cognac lactones **22**[5,6] which can be obtained in a well documented cuprate addition corresponded to the configurations given in the literature.



These first results indicate very clearly that cycloadducts generated from optical active dienes can easily be taken through a sequence of highly diastereoselective and regioselective steps to later yield very pure enantiomers in a highly efficient and non racemizing thermal Retro process. The very high chemical flexibility of this technique has been demonstrated already in our laboratory with a large number of quite different cycloadducts and these results will be communicated in the near future

EXPERIMENTAL

^{1}H-NMR spectra were obtained using a Bruker AM 300 and a WP 200 spectrometer with TMS as internal standard. IR spectra were obtained using a Perkin-Elmer 457 spectrometer. UV spectra were obtained using a Beckman 3600 spectrometer Mass spectra were obtained using a Finnigan MAT 312 spectrometer at 70eV. Optical rotations were obtained with a Perkin-Elmer 241 spectrometer. Melting points were taken using a Leitz 350 and are uncorrected.

1-Phenyl-7a-methyl-4,5,6,7-tetrahydroinden 2: 210 mg of diene **3** (1 mmol) is dissolved in 10 ml anhydrous dimethyl sulfoxide and at 0°C treated with 130 mg (1.1 mmol) potassium tert.butylate. The dark violet reaction mixture is stirred at 0°C for 1 h. For work up saturated ammonium chloride solution is added and the diene is extracted with methyl tert.butylether. The combined extracts are washed with brine, dried with magnesium sulfate and evaporated to yield a brown oil. This is filtered over silica and with petrolether 155 mg (74%) of pure diene **2**[1] are obtained.

Butynone adduct 4_2: Diene **2** (10 mmol) is dissolved in anhydrous CH_2Cl_2 (50 ml) and 15 mmol butynone is added. This mixture is left at 6.5 kbar for 48 h at r.t. The crude reaction mixture is filtered through silica gel (Et_2O/hexane 1 : 3) and the solvent is removed in vacuo. Yield: 20%, m.p. 135°C. ^1H NMR (C_6D_6, TMS): δ 6.78 (1) s, 7.02-7.28 (5) m, 6.90 (1) d, J = 5 Hz, 6.28 (1) d, J = 5 Hz, 1.94 (3) s, 0.92 (3) s broad. IR ($CHCl_3$): 1660, 1540 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O$ (278.4): C, 86.29; H, 7.96 Found: C, 86.28; H, 7.98.

General procedure for the cuprate additions: To a thienyl cuprate solution (5 mmol) prepared according to the Lipshutz procedure , 3 ml of a 1,6M solution of the corresponding lithiumalkyl is slowly added at -78°C. After 10' at -78°C 2 mmol of the corresponding butynone adduct dissolved in 6 ml anhydrous THF is added with a syringe. The temperature is kept at -78°C for another 30' and then raised to r.t. The reaction mixture is then added to saturated ammonium chloride solution and extracted with dichloromethane. The combined extracts are washed with brine, dried with magnesium sulfate and provided after evaporation of the solvent the ketones **6a** and **6b** in 80% and 85% yield, respectively

6a: m.p 162°C. ^1H-NMR ($CDCl_3$, TMS): δ 7 4-7.1 (6) m, 6.6-6.7 (2) m, 6.31 (1) d, J = 6 Hz, 6.06 (1) d, J = 6 Hz, 3.78 (3) s, 3.62 (1) d, J = 4.5 Hz, 1.91 (3) s, 1.34 (3) d,,J = 7.5 Hz, 1.0 (3) s, IR (KBr). 1705, 1610, 1580, 1500 cm^{-1}. MS (110°C): M^+ = 426 (12%), 342 (100), 326 (26). Anal. Calcd for $C_{30}H_{34}O_2$ (426.6): C, 84 47; H, 8.03. Found: C, 84.07; H, 8.06.

6b m.p. 153°C. ^1H-NMR ($CDCl_3$, TMS): δ 7.1-7.4 (6) m, 6.6-6.8 (2) m, 6.38 (1) d, J = 6 Hz, 5.93 (1) d, J = 6 Hz, 3.78 (3) s, 3.65 (1) d, J = 4.5 Hz, 1.83 (3) s, 1.01 (3) s, 0.8 (3) tr, J = 6 Hz. IR (KBr). 1705, 1610, 1575, 1500 cm^{-1}. MS (130°C): M^+ = 468 (29%), 342 (100), 186 (39). Anal. Calcd for $C_{33}H_{40}O_2$ (468.7). C, 84.53; H, 8.56. Found: C, 84.00; H, 8.41.

General procedure for the prepartion of acetates 7 In an oven-dried flask 1 mmol of a ketone **6** is dissolved in 25 ml anhydrous THF Under argon 1.5 mmol of a fresh commercial solution (Aldrich) of L-selectride is added at -78°C and the mixture is kept at this temperature for another 30' and after this warmed up to r.t The progress is checked by TLC and as soon as the reaction is finished it is poured into 1M citric acid and extracted with dichloromethane. The combined extracts are washed with sodium bicarbonate solution and brine, dried with magnesium sulfate and evaporated. The crude oily alcohol obtained this way is treated overnight with acetic acid anhydride (20ml) to give rise to a quantitative yield of the corresponding acetate on evaporation of the anhydride.

7a m.p. 148°C ^1H-NMR ($CDCl_3$, TMS): δ = 7.1-7.4 (6) m, 6 60-6.75 (2) m, 6.28 (1) d, J = 5 Hz, 6.12 (1) d, J = 5 Hz, 4.70 (1) m, 3.78 (3) s, 1.15-1.30 (9) m, 1.08 (3) s, 1.00 (3) s. IR (KBr): 1730, 1610, 1580, 1500 cm^{-1} MS (110°C): M^+ = 470 (29%), 410 (58), 342 (100). Anal. Calcd for $C_{32}H_{38}O_3$ (470.6)· C, 81 79, H, 8 14 Found: C, 81.72; H, 8.14.

Heating this compound to 250°C in vacuo yielded after redistillation in a Büchi Kugelrohr oven 85% of acetate **8a** identical to a synthetic sample (see below) rotation values included. In the same way a 90% yield of **8b** was obtained from **6b**. The diphenyl phosphinoxides of type **9** were prepared according to

Horner's method (**9a**[7]); **9b** yield: 94%, m.p.: 72°C. ^{1}H-NMR ($CDCl_3$, TMS): δ = 0.84 (3) tr, J = 6.5 Hz), 1.30 (4) m, 1.60 (2) m, 2.24 (2) m, 7.39-7.82 (10) m. Anal. Calcd for $C_{17}H_{21}OP$ (272.1): C, 75.00; H, 7.77. Found: C, 74.55, H, 7.62.

Preparation of the ketophosphine oxides 11: 10 mmol of the corresponding phosphine oxide dissolved in 50 ml of anhydrous THF is treated with 10 mmol of butyllithium at 0°C. The reaction mixture is taken to -78°C and 10 mmol mof tert.butyl dimethylsilyl protected S-methyl lactate is added slowly. After 2 h the mixture is hydrolysed and the THF is evaporated in vacuo. The residue is extracted with dichloro methane, the combined extracts are washed with brine, dried with magnesium sulfate and evaporated to give **11a** and **11b** in 90% and 55% yield, respectively.

11a: ^{1}H-NMR ($CDCl_3$, TMS): δ = 0.03, 0.04, 0.06 u. 0.07 (6), s, 0.88, 0.91 (9) s, 1.20 (3) d, J = 6.5 Hz, 1.28-1.33 (3) m, 4 12, 4.23 (1) q, J = 6 5, 4.37 - 4.63 (1) m, 7.38-7.98 (10) m. IR ($CHCl_3$): 1710, 1435, 1180, 1120 cm^{-1}. MS (80°C): M^+ = 416 (4%), 401 (4), 360 (27), 359 (100), 339 (12), 230 (12), 229 (93), 156 (90). HRMS Calcd for $C_{23}H_{33}O_3PSi$: 416.1936. Found: 416.1935

11b: ^{1}H-NMR ($CDCl_3$, TMS). δ = 0 04 (3) s, 0.08 (3) s, 0.50-1.26 (21) m, 3.96 (1) q, J = 6 5 Hz, 4.42-4.69 (1) m, 7.39-8.93 (10) m. IR ($CHCl_3$): 1710, 1435, 1255, 1150, 1115 cm^{-1}. MS (80°C): M^+ = 458 (4%), 457 (5), 443 (5), 402 (29), 401 (100), 381 (25), 357 (16), 272 (68), 228 (75), 201 (51), 198 (64) HRMS Calcd for $C_{26}H_{39}O_3PSi$: 458.2406. Found: 458.2405.

Preparation of the S-Acetates 8a amd 8b: 3 mmol of the ketophosphine oxyde is dissolved in 40 ml anhydrous methanol and 114 mg sodium borohydride is added slowly at 0°C. The mixture is stirred overnight at r.t. and then directly separated by chromatography on silica. The fractions eluted with petrolether/acetone (3 : 1) are collected and provided after evaporation of the solvent the threo alcohols **12a** (91%) and **12b** (87%). These are redissolved in 60 ml anhydrous dimethyl formamide and treated with two equivalents sodium hydride (80% suspension in mineral oil) at r.t. After 16 h the mixture is poured into icecold 1M citric acid and extracted with ether. The silylethers obtained on evaporation of the solvent in vacuo are immediately dissolved in 15 ml THF and 4.5 ml of a 1M tetrabutylammonium fluoride solution in THF is added. After 2 h at r.t. the THF is removed in vacuo and replaced by 15 ml anhydrous dichloromethane. 3 ml dry pyridine, 1.5 ml acetic acid anhydride, and 100 mg 4-dimethylamino pyridine is added and the mixture is stirred at r.t. for 5 h. For work up it is poured into 2M citric acid and extracted with dichloromethane. The combined extracts are washed with saturated sodium bicarbonate and brine, dried with magnesium sulfate, and evaporated. The oily residue is purified by Kugelrohr distillation and after this proved to be identical in every detail to the products of the retro-Diels-Alder process including optical rotation values.

8a: Yield 51%. ^{1}H-NMR ($CDCl_3$, TMS): δ = 1 28 (3) d, J = 6.5 Hz, 1.68 (3) d, J = 6 Hz, 2 03 (3) s, 5.28 (1) m, 5.47 (1) m, 5.73 (1) m. IR ($CHCl_3$): 1725, 1445, 1380, 1250, 910 cm^{-1}. MS (r.t.): M^+ = 128 (3%), 113 (10), 86 (27), 85 (13), 69 (29), 43 (100). HRMS Calcd for $C_7H_{12}O_2$: 128.0837. Found: 128.0837. $[\alpha]_D^{20^\circ}$ = -55 (-54 from retro diene).

8b: Yield 98%. ^{1}H-NMR ($CDCl_3$, TMS): δ =0.83-1.44 (7) m, 1.28 (3) d, J = 6 Hz, 1.95-2.10 (5) m, 5.31 (1) m, 5.44 (1) m, 5.68 (1) m. IR ($CHCl_3$): 1720, 1370, 1250, 1040 cm^{-1}. MS (r.t.): M^+ = 170 (0.5%), 169 (1), 154 (3), 147 (8), 128 (26), 127 (6), 43 (100). HRMS Calcd for $C_{10}H_{18}O_2$: 170.1306. Found: 170.1306. $[\alpha]_D^{20°}$ = -63 (-64 from retro diene).

Preparation of lactones 16 and 17: 1 Mmol of the maleic anhydride adduct 5_1 or 5_2 is dissolved in 10 ml dry toluene and 1.2 mmol of the corresponding Grignard reagent (1M ether solution) is slowly added at -78°C. After 15' the reaction mixture is allowed to reach r.t. and stirred for another 15 '. The progress is checked by TLC and after consumption of the starting material the mixture is poured into saturated aqueous ammonium chloride solution and extracted with dichloromethane. The combined extracts are dried with magnesium sulfate and evaporated in vacuo. The crude residue is redissolved in 6 ml anhydrous dichloromethane and 6 ml trifluoroacetic acid and at 0°C 1.2 ml triethyl silane (Merck) is added The mixture is stirred for 4 h, for work up treated with saturated sodium bicarbonate solution and extracted with dichloromethane. The combined extracts are washed with brine, dried with magnesium sulfate, and evaporated. The oily residue obtained this way is triturated with ether to yield white crystals of the corresponding lactones.

16a (R = CH_3): Yield 86%, m p. 227-228°C. ^{1}H-NMR ($CDCl_3$, TMS): δ = 0.81 (3) s, 1.07 (3) d, J = 7 Hz, 3 48 (1) d, J = 8 Hz, 3.78 (3) s, 4.04 (1) tr, J = 8 Hz, 4.76 (1) m, 6.36 (2) s, 6.7 (2) m, 7.29 (1) d, J = 8 Hz, 7 22-7.45 (5) m,. IR (KBr): 1760, 1610, 1580, 1500 cm^{-1}. MS (180°C): M^+ = 440 (7%), 342 (100), 186 (40). Anal. Calcd for $C_{30}H_{32}O_3$ (440.6): C, 81 78; H, 7.31. Found. C, 81.57; H, 7.19.

16b (R = C_2H_5): Yield 88%, m.p. 243°C. ^{1}H-NMR ($CDCl_3$, TMS): δ = 0.83 (3) s, 0.87 (3), tr, J = 7 Hz, 3 48 (1) d, J = 8 Hz, 4.05 (1) tr, J = 8 Hz, 4.46 (1) m, 6.33 (2) s, 6.68 (2) m, 7.18 (1) d, J = 8 Hz, 7.28-7.43 (5) m,. IR (KBr): 1760, 1610, 1580, 1500 cm^{-1}. MS (180°C): M^+ = 454 (9%), 342 (100), 186 (36). Anal. Calcd for $C_{31}H_{34}O_3$: C, 81.90; H, 7.53. Found: C, 81 65, H, 7.44.

16c (R = i-C_3H_7): Yield 96%, m.p 217°C. ^{1}H-NMR ($CDCl_3$, TMS): δ = 0.44 (3) d, J = 6 Hz, 0.90 (3) d, J = 6 Hz, 0.98 (3) s, 3.51 (1) m, 3.78 (3) s, 4.02 (1) m, 6.3 (1) d, J = 6 Hz, 6.48 (1) d, J = 6 Hz, 6.70 (2) m, 7.18 (1) d, J = 8 Hz, 7.25-7 43 (5) m. IR (KBr): 1760, 1610, 1580, 1500 cm^{-1}. MS (160°C): M^+ = 468 (29%), 342 (100), 186 (62) HRMS Calcd for $C_{32}H_{36}O_3$: 468.2664. Found: 468.2662. Anal. Calcd for $C_{32}H_{36}O_3$ (468.3). C, 82.02; H, 7 74. Found C, 81.75; H, 7.59.

16d (R = i-C_4H_9): Yield 68%. ^{1}H-NMR ($CDCl_3$, TMS): δ = 0.70 (3) d, J = 6 Hz, 0.72 (3) d, J = 6 Hz, 0.83 (3) s, 3.46 (1) d, J = 8 Hz, 3 79 (3) s, 4.04 (1) tr, J = 8 Hz, 4.65 (1) m, 6.32 (2) s, 6.70 (2) m, 7.18 (1) d, J = 8 Hz, 7.25-7.44 (5) m. IR (KBr): 1760, 1610, 1580, 1500 cm^{-1}. MS (160°C): M^+ = 482 (12%), 342 (100). Anal. Calcd for $C_{33}H_{38}O_3$ (482.7): C, 82.12; H, 7.93. Found: C, 81.78; H, 7.87.

16e (R = C_4H_9): Yield 86%, m.p. 228°C. ^{1}H-NMR ($CDCl_3$, TMS): d = 0.71 (3) tr, J = 7 Hz, 0.83 (3) s, 3.45 (1) d, J = 8 Hz, 3.78 (3) s, 4.04 (1) tr, J = 8 Hz, 4.55 (1) m, 6.33 (2) s, 6.69 (2) m, 7.18 (1) d, J = 8 Hz, 7.28-7.45 (5) m. IR (KBr): 1760, 1610, 1580, 1500 cm^{-1}. MS (210°C): M^+ = 482 (91%), 342 (100), 307 (95). HRMS Calcd for $C_{33}H_{38}O_3$: 482.2820. Found: 482.2822. Anal. Calcd for $C_{33}H_{38}O_3$ (482.3): C, 82.12; H, 7.93. Found: C, 81.94; H, 7.78.

17a (R = CH_3): Yield 31%, m.p.161°C. ^{1}H-NMR ($CDCl_3$, TMS): δ = 0.61-0.76 (1) m, 0.82 (3) s, 1.05-1.78 (5) m, 1.43 (3) d, J = 7 Hz, 1.94-2.16 (2) m, 2.96 (1) tr, J = 8 Hz, 4.16 (1) d, J = 8 Hz, 4.73 (1) dq, J = 8 Hz, J = 7 Hz, 6.20 (1) d, J = 6 Hz, 6.29 (1) d, J = 6 Hz, 7.21-7.43 (5) m. IR ($CHCl_3$): 2941, 1756, 1499, 1446, 1384, 1358, 1180 cm^{-1}. MS (110°C): M^+ = 308 (4.5%), 307 (19), 236 (39), 221 (52), 210 (100). HRMS Calcd for $C_{21}H_{24}O_2$: 308.17763. Found: 308.17775.

17b (R = C_4H_9): Yield 58%. ^{1}H-NMR ($CDCl_3$, TMS): δ = 0.64-0.70 (1) m, 0.80 (3) s, 0.91 (3) tr, J = 7 Hz, 1.04-1.83 (11) m, 1.93-2.14 (2) m, 2.98 (1) tr, J = 8 Hz, 4.14 (1) d, J = 8 Hz, 4.45-4.59 (1) m, 6.18 (1) d, J = 6 Hz, 6.24 (1) d, J = 6 Hz, 7.2-7.43 (5) m. IR ($CHCl_3$): 2960, 2938, 1750, 1600, 1500, 1465 cm^{-1}. MS (25°C): M^+ = 350 (1%), 236 (2), 104 (8), 103 (79), 75 (100). HRMS Calcd for $C_{24}H_{30}O_2$: 350.4998. Found: 350.4998.

For retro diene reactions 5 mmol of these lactones is quickly heated in a Büchi Kugelrohr apparatus to 250°C. The thermolysis product is collected in a dry ice/acetone cooled Kugelrohr and redistilled to give a 85-90% yield of the corresponding butenolide.

Butenolide S-18 R = CH_3 see **18a** angelica lactone
Butenolide S-18 R = C_2H_5 = **18b**[8]
Butenolide S-18 R = i-C_3H_7 = **18c**[9]
Butenolide S-18 R = C_4H_9 = **18d**[3]
Butenolide S-18 R = i-C_4H_9 = **18e**

^{1}H-NMR ($CDCl_3$, TMS): δ = 0.95 (3) d, J = 6.5 Hz, 1.01 (3) d, J = 6.5 Hz, 1.55 (2) tr, J = 6 Hz, 1.90 (1) m, 5.09 (1) m, 6.09 (1) dd, J = 6 Hz, J = 2 Hz, 7.49 (1) dd, J = 6 Hz, J = 2 Hz. IR ($CHCl_3$): 1165, 1745, 1760 cm^{-1}. $[\alpha]_D^{20°}$ = +82.5 .

(+)S-Angelica lactone 18a: A solution of 745 mg (2.5 mmol) bis(2,2,2-trifluoro ethyl)carboxymethyl phosphonate (Still reagent) and 2.0 g (7.6 mmol) 18-crown-6 in 50 ml anhydrous THF under argon is cooled to -78°C and treated with 2.5 mmol KN(TMS)$_2$ (0.5M solution in toluene). 395 mg (2.5 mmol) THP-protected S-lactaldehyde **19** (2.5 mmol) is added and the mixture is stirred at -78°C for 1.5 h. After this saturated ammonium chloride solution is added followed by extraction with ether. The combined ether extracts are dried with magnesium sulfate and after evaporation of the solvent the oily residue is purified by flash chromatography to yield 508 mg (95%) of a colourless oil with petrolether/ether (4 : 1) which was proven to be the unsaturated ester **21** by the following spectroscopic data.

^{1}H-NMR ($CDCl_3$, TMS): δ = 1.28 and 1.31 (3) d, J = 6.5 Hz, 3.71 and 3.72 (3) s, 5.71 and 5.82 (1) dd, J = 11 Hz, J = 1.5 Hz, 6.15 and 6.36 (1) dd, J = 11 Hz, J = 8 Hz, 5.36 (1) m. All signals occur twice owing to epimers coused by the THP ether group. IR ($CHCl_3$): 1719, 1127, 1074, 1033, 1027 cm^{-1}. MS (r.t.): M^+-101 = 113 (21), 101 (10), 85 (100). 103 mg of this oil (0.48 mmol) is dissolved in 3 ml dichloromethane and treated with 9 mg p-toluene sulfonic acid. The mixture is left at r.t. for 16 h, the solvent is after treatment with 20 mg sodium carbonate removed in vacuo and the residue filtered over silica (petrolether/ether 1 : 1). For final purification the material obtained this way is distilled in a Büchi Kugelrohr apparatus to yield 28 mg (60%) of a slightly yellow oil which proved to be pure angelica lactone.

^{1}H-NMR ($CDCl_3$, TMS): δ = 1.44 (3) d, J = 7 Hz, 5.13 (1) q, tr, J = 6 Hz, J = 1.8 Hz, 6.08 (1) dd, J = 6 Hz, J = 1.8 Hz, 7.46 (1) dd, J = 6 Hz, J = 1.8 Hz.

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