FROM STEROIDS TO MACROLIDES#1

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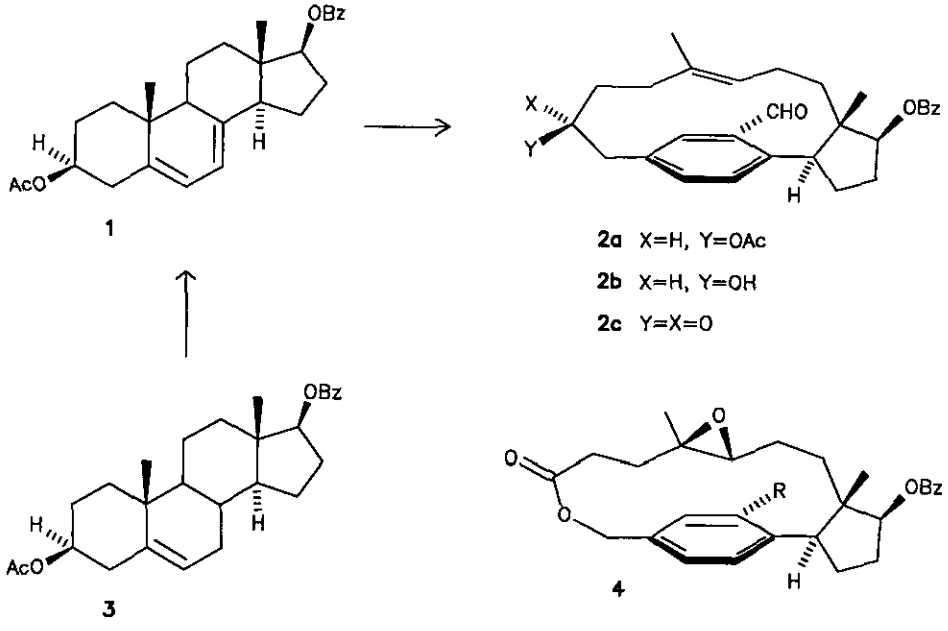
#Dedicated to Professor Sir Derek Barton at the occasion of his 70th birthday.

Abstract - Ansa-seco steroids of type **2** - easily obtained from ring B 5,7-butadienes - are shown to undergo stereoselctive epoxidation reactions and regioselective Baeyer-Villiger oxidations to form 15-membered lactones.

As we recently noticed the very easy formation of ansa-seco steroids of type **2** from ring-B butadienes in a Diels-Alder retro-Diels-Alder sequence,[2] we decided to investigate the formation of the corresponding macrolides (e.g. **4**) in Baeyer-Villiger oxidations of the 3-keto derivatives **2c**.

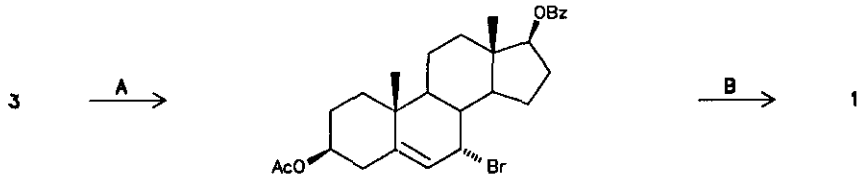
Scheme I



1. Formation of Butadienes

In order to have easy access to these butadienes from a cheap bulk material, we performed a thorough *investigation of the well documented* bromination-elimination sequence with diester **3**.[3] This compound is one of the products from the large scale side-chain degradation of sitosterol, which is an industrial process providing annually roughly one thousand tons of this steroid.[4] Although this elimination has been widely used, reported yields are in some cases[5] not satisfactorily for the preparation of starting materials. Extensive variation of reaction conditions (see Table 1) revealed that both the choice of the halogenating reagent as well as that of the correct base for the elimination reaction are crucial for a high yield in this sequence; the combination of a free radical halogenation (AIBN, N-dibromedimethylhydatoine) with a base catalyzed (quinaldine) elimination process providing the best results.

Table I



A	B			
	Catalyst	Time	Yield	
AIBN, 1,3-dibromo-5,5-dimethylhydantoine in hexane 1 h irradiation	1. DBU (1.5 eq.)	16 h	0	a
	2. $P(OCH_3)_3$ (3 eq.)	1.5 h	55%	b
	3. collidine (10 eq.)	2 h	44%	b
	4. α,α'-bis-tert.butyl-pyridine (1.5 eq.)	2 h	64%	b
	5. quinaldine (10 eq.)	1 h	81%	b
	6. $(C_4H_9)_4NBr$ (0.025 eq.)	0.8 h		
	$(C_4H_9)_4NF$ (6.5 eq.)	0.5 h	71%	c

[a] reflux in dichloromethane, formation of the 2,4,6-triene

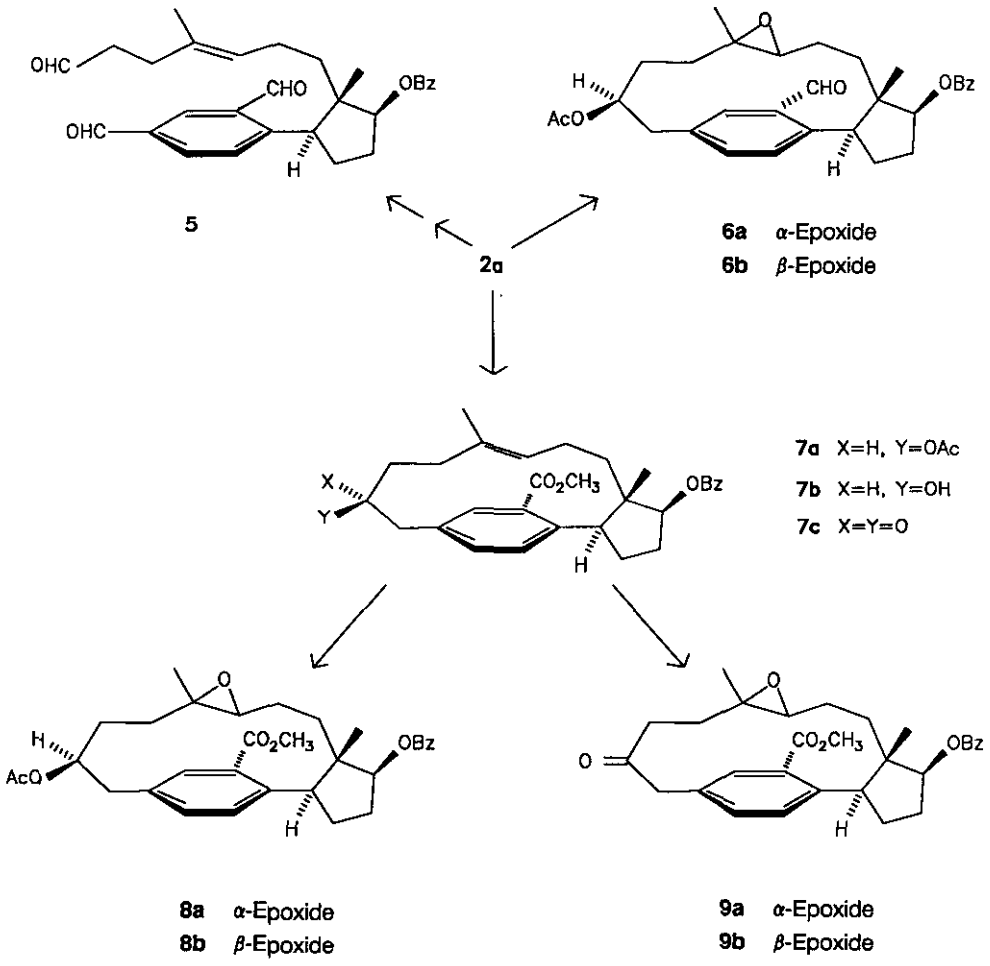
[b] reflux in xylene

[c] in tetrahydrofurane at room temperature

2. Diels-Alder Cycloadditions

Having easy access to the butadiene, the next aim was to investigate a variety of acetylenic dienophiles and so we compared methyl propiolate, cyanoacetylene, propargylic aldehyde and butynone to find out that only propargylic aldehyde and butynone gave high yields of cycloaddition products. As the aldehyde provides more chemical flexiblity we concentrated completely, on this dienophile ending up with a reliable yield exceeding 80% for seco-aldehyde **2a**. Although keto-aldehyde **2c** could be generated from **2b** in a quite simple PCC-oxidation, a few drawbacks with the aldehyde series made us change our minds about this functional group. First of all, the oxidation to form ketone **2c** was accompanied by the formation of **5** resulting from oxidative

Scheme II

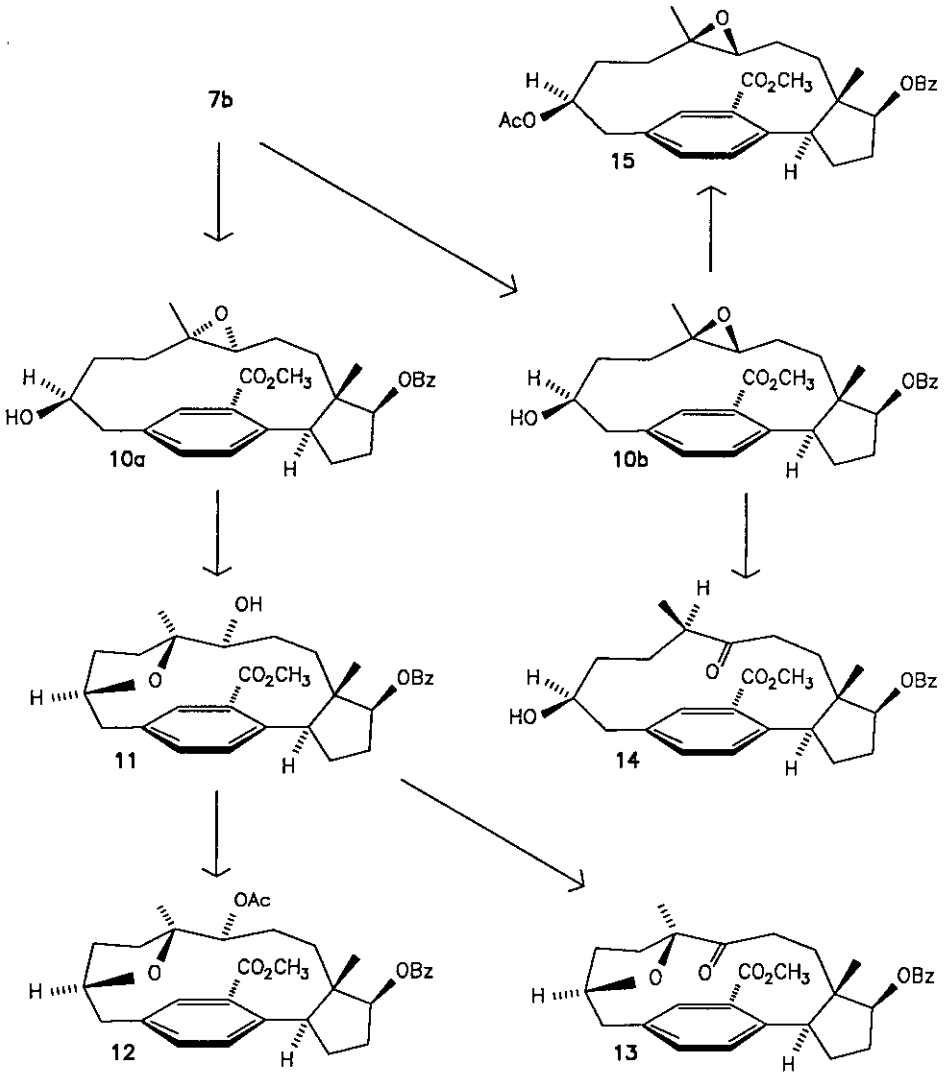


ring splitting. Much more disappointing, however, was the observation that **2a** on treatment with m-chloroperbenzoic acid gave rise to a 2 : 1 mixture of both epimeric epoxides **6** which we were unable to separate by normal chromatographic techniques. As epoxide formation can safely be predicted to be the first process under Baeyer-Villiger conditions we changed to methyl ester **7a** hoping for higher stability and higher selectivity in the epoxidation process. Methyl ester **7a** was formed in a PCC-oxidation of the cyanohydrin of **2a** followed by methanolysis and with this material investigations into the stereoselectivity of epoxidation processes were given first priority.

3. Stereoselective Epoxide Formation

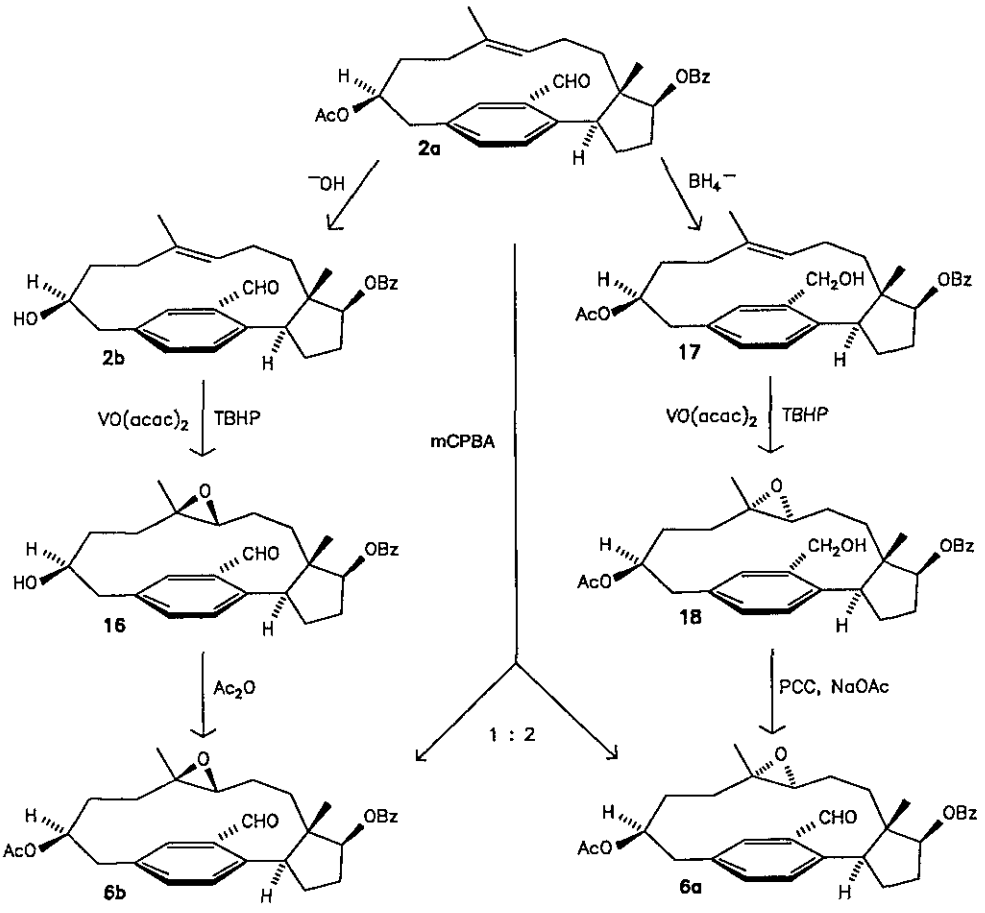
In order to have available a set of derivatives with different polarities, acetate **7a** was selectively hydrolyzed to the corresponding alcohol **7b** which was smoothly oxidized to the cyclic ketone **7c**. Although the epoxidation of this ketone proved to be a very efficient transformation, the selectivity was even lower in this case, a 1 : 1 mixture of epimeric epoxides resulting on treatment with m-chloroperbenzoic acid in dichloromethane. The only advantage with this reaction turned out to be the fact that both epoxides could be separated by column chromatography. Selectivity improved slightly with acetate **7a**, which gave rise to a separable 1 : 1.5 mixture of epoxides, but, as this is of course useless for preparative work, we switched to alcohol **7b** hoping that hydrogen bonding would direct the epoxidation process. Although unfortunately, the selectivity was again low (1 : 1.6), this particular epoxidation was followed by a quite efficient stereospecific tetrahydrofuran formation in an intramolecular nucleophilic ring opening of the epoxy group, which provided chemical evidence for the absolute configuration of these compounds. As only one of the two epimers behaved in this manner it was assumed that this should be α-epoxide **10a**. Only with this combination of configurations is nucleophilic displacement of the epoxide possible, allowing formation of tetrahydrofuran **11**. As expected, hydroxy ether **11** formed an acetate (**12**) and PCC-oxidation of **11** generated ketone **13** in 93% yield. The other stereoisomer (**10b**) after acetylation proved to be identical with the minor oxidation product from acetate **7a**, thus indicating the β-configuration for this compound too. Quite impressed by the stereospecificity of this epoxide opening, we treated β-epoxide **10b** with BF_3 just to note that this rearrangement was also regioselective and stereospecific. As an α-hydrogen has to migrate in this transformation configuration **14** was assigned to this ketone. Encouraged by the fact that under certain conditions highly stereoselective processes are observed at these centres, we applied the Sharpless epoxidation[5] to the secondary alcohol **7b** and were very pleased to note that the stable β-epoxide **10b** was formed in 63% yield exclusively in this case.

Scheme III



Obviously the well established directing effect of the hydroxy group is operating satisfactorily in this transformation too and so acetate **2a** was hydrolyzed selectively to the secondary β-alcohol **2b** which was treated under the same conditions. This time the reaction proved to be highly stereoselective again resulting exclusively in epoxide **16**. Subsequent acetylation proved the compound to be identical with the minor reaction product from the epoxidation of acetate **2a**.

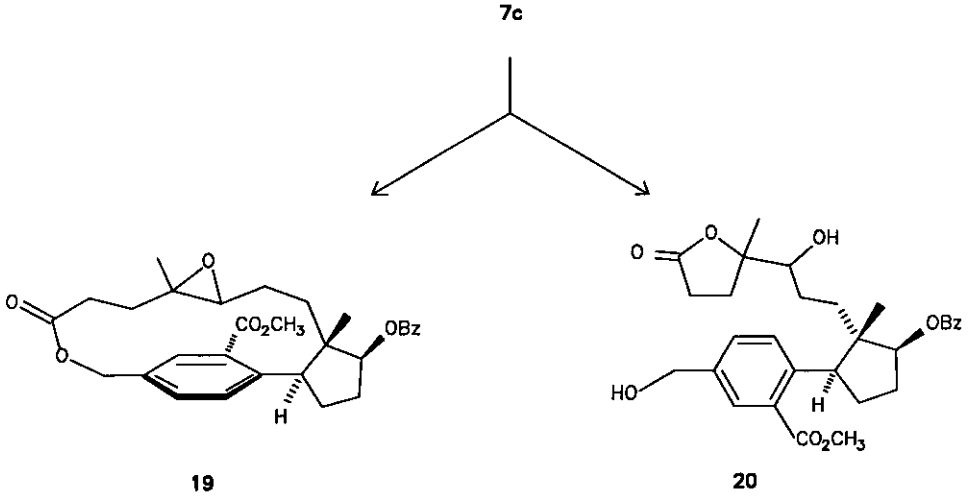
Scheme IV



As conformational data from X-ray and nmr investigations pointed to α-directed attack on the double bond by substituents at the aromatic ring, we reduced the benzaldehyde with borohydride and were pleased to note that, starting with benzyl alcohol **17**, only one epoxide (**18**) was once again formed with excellent stereoselectivity. Reoxidation of this product to the corresponding aldehyde proved it to be identical with the major epoxide from a direct epoxidation of **2a**.

Having stereoselective epoxidation processes available, we started a first series of experiments with ketone **7c** aiming at epoxy-lactones. As mentioned above a mixture of two epoxides was initially generated under Baeyer-Villiger conditions. Further treatment with peracid, however, gave rise to two lactones as expected.

Scheme V



After isolation, one of these lactones (**19**) was shown to have an epoxide-lactone structure (see Scheme V), while the other compound proved to be diol **20**. Again a highly stereospecific transformation must be involved as we at the moment do not know the exact configurations of these products, the discussion of this result has to be postponed until correlation to **6a** and **6b** establishes the configurations of these lactones.

ACKNOWLEDGMENTS

Substantial help from the DFG (Wi 206/38-2) and the Fonds der Chemischen Industrie is gratefully acknowledged.

Thanks are due to Dr.H.Laurent and Professor Dr.Dr.h.c.R.Wiechert of Schering Aktiengesellschaft, Berlin, for a constant and very generous supply of diester **3**.

EXPERIMENTAL

^{1}H Nmr spectra were recorded with a Bruker AM 300 and a WP 200 using TMS as internal standard. Ir and uv spectra were taken with a Perkin-Elmer 457 and a Beckman 3600, respectively. For mass spectroscopy a Finnigan MAT 312 was used at 70 eV and the temperatures indicated. Optical rotations were measured with a Perkin-Elmer 241 in chloroform, and melting points were taken with a Leitz 350.

General procedure for the formation of 5,7-dienes (1): 2.3 mmol of diester **3** are dissolved in 80 ml of n-hexane, and then 1.8 mmol of 1,3-dibromo-5,5-dimethylhydantoine and 0.12 mmol of AIBN were added and the mixture was irradiated with a 500 W photolamp for 1 h. The solution was brought to room

temperature, filtered and evaporated. The remaining residue was dissolved in 40 ml of dry xylene, 10 equivalents of quinaldine (or other bases as given in Table 1) was added, and the mixture was refluxed till completion of the reaction (TLC control, reaction times and yields see Table 1). The cold reaction mixture was filtered and diluted with methyl tert.butyl ether and washed with dilute aqueous citric acid, sodium bicarbonate solution, and brine, dried over sodium sulfate and evaporated. The crude material was purified by flash chromatography with petrol ether-methyl tert.butyl ether (5:1).

5,7-Bisdehydro-3β-acetoxy-17β-benzoyloxy-androstane (1): mp 107 °C; $[\alpha]_D^{22}$ = -18 ° (c = 0.63, $CHCl_3$). Uv (CH_3OH): 231,270,281 nm. Ir (KBr): 1710,1725,1270,1240 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.84-2.61 (m,16H), 0.89 (s,3H), 0.98 (s,3H), 2.06 (s,3H), 4.62-4.82 (m,1H), 4.96 (dd,J=7Hz,J=9Hz,1H), 5.40-5.50 (m,1H), 5.56-5.66 (dd,J=2Hz,J=6Hz,1H), 7.39-7.63 (m,3H), 8.00-8.10 (m,2H). Ms (70 eV,140 °C): m/z (%) = 434 (M^+,2), 375 (22), 374 (71), 359 (14), 269 (16), 252 (29), 237 (21), 143 (18), 105 (100), 77 (26).

Ms Calcd for $C_{28}H_{34}O$: 434.2457. Found: 434.2457.

Anal. Calcd for $C_{28}H_{34}O_4$: C, 77.42; H, 7.83: Found: C, 77.34; H, 7.78.

General procedure for the cycloadditon-aromatization sequence: To a solution of 10 mmol of diene **1** in 25 ml of dichloromethane, 10 mmol of boron trifluoride etherate and 20 mmol of propargylic aldehyde were added at 0 °C. After 30 min the mixture is poured into cold sodium bicarbonate solution. After extraction with dichloromethane and evaporation of the solvent the residue was dissolved in xylene and refluxed for 2 h. After evaporation of the solvent in vacuo the residue was purified by flash chromatography with petrol ether-methyl tert.butyl ether (3:1) to give rise to a quantitative yield of seco-compound **2a**: mp 128 °C, $[\alpha]_D^{21}$ = +85.2 ° (c = 0.670, $CHCl_3$). Ir (KBr): 2740, 1725,1700,1280,1250 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.81-2.62 (m,12H), 1.00 (s,3H), 1.25 (s,3H), 2.10 (s,3H), 2.72 (dd,J=8Hz,J=14Hz,1H), 3.46 (dd,J=6Hz, J=14Hz,1H), 3.62-3.75 (m,1H), 4.18 (t,J=10Hz,1H), 4.80-4.97 (m,1H), 5.07 (t,J=9Hz,1H), 7.37-7.65 (m,5H), 7.75 (s,1H), 8.02-8.13 (m,2H), 10.41 (s,1H). Ms (70 eV, 160 °C): m/z (%) = 488 (M^+,8), 366 (24), 306 (29), 288 (7), 105 (100), 77 (27).

Ms Calcd for $C_{31}H_{36}O_5$: 488.2563. Found: 488.2559.

Anal. Calcd for $C_{31}H_{36}O_5$: C, 76.23; H, 7.38. Found: C, 76.40; H, 7.14.

Selective hydrolysis: 0.4 mmol of **2a** dissolved in 5 ml of dichloromethane was mixed with 2.5 ml of a 0.4% solution of sodium methoxide in methanol and kept for 5 days at -20 °C. This gave after work up (addition to 20% aqueous citric acid, extraction with dichloromethane) an 88% yield of hydroxybenzoate **2b**: Ir ($CHCl_3$): 3620, 3400,2750,1720,1285,1125 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 1.02 (s,3H), 1.11-2.04 (m,9H), 1.27 (s,3H), 2.07-2.25 (m,2H), 2.38-2.60 (m,1H), 2.68 (dd,J=8Hz,J=13Hz,1H), 3.37 (dd,J=6Hz,J=13Hz,1H),

3.55-3.65 (m,1H), 3.82-3.97 (m,1H), 4.12 (t,J=10Hz,1H), 5.07 (t,J=9Hz,1H), 7.40-7.63 (m,5H), 7.69 (s,1H), 8.01-8.11 (m,2H), 10.43 (s,1H). Ms (70 eV, 160 °C): m/z (%) = 446 (M^+,4), 324 (21), 306 (10), 195 (11), 105 (100), 77 (35).

Ms Calcd for $C_{29}H_{34}O_4$: 446.2457. Found: 446.2457.

Subsequent PCC-oxidation: 0.64 mmol of **2b** in 3 ml of dry dichloromethane was added to a suspension of 1.3 mmol of PCC in 20 ml of dry dichloromethane and left at room temperature for 1.5 h. Filtration through a silica column gave rise to keto-benzoate **2c** (yield 64%). Ir ($CHCl_3$): 2760,1710,1285,1125 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 1.03 (s,3H), 1.26 (s,3H), 1.43-2.35 (m,11H), 2.40-2.61 (m,1H), 3.65 (d,J=16Hz,1H), 3.81 (d,J=16Hz,1H), 3.85-3.95 (m,1H), 4.17 (t,J=10Hz,1H), 5.09 (t,J=9Hz,1H), 7.41-7.65 (m,5H), 7.78 (m,1H), 8.03-8.11 (m,2H), 10.47 (s,1H). Ms (70 eV, 150 °C): m/z (%) = 444 (M^+,4), 443 (13), 323 (13), 322 (49), 195 (30), 105 (100), 77 (32).

Ms Calcd for $C_{29}H_{32}O_4$: 444.2301. Found: 444.2300.

As a minor byproduct a few mg of aldehyde **5** was isolated the possible structure of which was indicated by spectroscopic data. **5**: Ir ($CHCl_3$): 2740,1700,1275,1115 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$) δ = 0.80-2.72 (m,12H), 0.91 (s,3H), 1.48 (s,3H), 4.28 (dd,J=9Hz,J=9Hz,1H), 4.95-5.07 (m,1H), 5.34 (dd,J=6Hz,J=8Hz, 1H), 7.41 - 7.65 (m,3H), 7.80 (d,J=8Hz,1H), 7.97-8.06 (m,2H), 8.09 (dd,J=2Hz,J=8Hz,1H), 8.36 (d,J=2Hz, 1H), 9.71 (t,J=2Hz,1H), 10.10 (s,1H), 10.44 (s,1H). Ms (70 eV, 110 °C): m/z (%) = 460 (M^+,2), 338 (4), 320 (8), 302 (5), 213 (54), 196 (16), 124 (29), 105 (100), 77 (30).

Standard epoxidation: 0.1 mmol of the corresponding trisubstituted olefin was dissolved in 5 ml of dichloromethane and treated with 0.2 mmol of m-chloroperbenzoic acid and 0.4 mmol of sodium bicarbonate for 15 min to generate epoxide **6** which was obtained in 88% yield as a 2 : 1 mixture of the α and β-epimer, respectively. For spectroscopic characterization see data for the pure diastereomers **6a** and **6b**.

2a → 6a + 6b (2:1) Ir ($CHCl_3$): 1710,1280,1250,1120 cm^{-1}. Ms (70 eV, 180 °C): m/z (%) = 504 (M^+,16), 486 (2), 382 (23), 322 (10), 304 (7), 105 (100), 77 (23).

6a: ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.70 (d,J=9Hz,1H), 0.75 - 2.30 (m,11H), 0.95 (s,3H), 1.08 (s,3H), 2.10 (s,3H), 2.43 - 2.65 (m,1H), 2.59 (dd,J=9Hz,J=13Hz,1H), 3.30 (dd,J=5Hz,J=13Hz,1H), 4.47 (t,J=10Hz,1H), 4.81 - 4.95 (m,1H), 5.10 (t,J=9Hz,1H), 7.38 - 7.62 (m,5H), 7.78 (d,J=2Hz,1H), 8.00 - 8.09 (m,2H), 10.28 (s,1H).

6b: ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.78 - 2.62 (m,13H), 0.97 (s,3H), 1.12 (s,3H), 2.11 (s,3H), 2.72 (dd,J=8Hz,J=13Hz,1H), 3.23 (dd,J=4Hz,J=13Hz,1H), 4.285 (dd,J=9Hz,J=11Hz,1H), 4.62 - 4.78 (m,1H), 5.12 (t,J=9Hz,1H), 7.33 - 7.66 (m,5H), 7.79 (d,J=2Hz,1H), 7.99 - 8.09 (m,2H), 10.35 (s,1H).

Methyl ester 7a: 1.67 g (3.42 mmol) of aldehyde **2a** dissolved in 3 ml of dry dichloromethane was after dilution with 100 ml of methanol treated with 1.67 g (34 mmol) of sodium cyanide and 1.5 ml of acetic acid. After 3 h the mixture was poured into water and extracted with dichloromethane. After evaporation of the solvent in vacuo the remaining colourless oil was redissolved in 5 ml of dichloromethane and added to a suspension of 1.5 g (6.9 mmol) of PCC in 50 ml of dry dichloromethane. This suspension was stirred for 17 h at room temperature, treated with 10 ml of dry pyridine and 5 ml of dry methanol, stirred for another two hours and filtered (silica column). The column was thoroughly washed with methyl tert.butyl ether and the combined phase was washed with 1N-HCl, aqueous sodium bicarbonate solution and brine. The residue obtained on evaporation of the solvent was purified by flash chromatography (petrol ether-methyl tert.butyl ether 6 : 1) to give rise to 1.21 g (68%) of methyl ester **7a**. Ir (KBr): 1719,1274,1246 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.80 - 2.55 (m,12H), 1.04 (s,3H), 1.28 (s,3H), 2.09 (s,3H), 2.62 (dd, J=8Hz,J=13Hz,1H), 3.38 (dd,J=6Hz,J=13Hz,1H), 3.76 (dd,J=8Hz,J=12Hz,1H), 3.91-4.01 (m,1H), 3.94 (s,3H), 4.78-4.98 (m,1H), 5.00 (t,J=9Hz,1H), 7.38 - 7.66 (m,6H), 8.00 - 8.12 (m,2H). Ms (70 eV, 180 °C): m/z (%) = 518 (M^+,6), 458 (9), 396 (28), 336 (45), 304 (18), 105 (100), 77 (28).
Ms Calcd for $C_{32}H_{38}O_6$: 518.2668. Found: 518.2668.
Anal. Calcd for $C_{32}H_{38}O_6$: C, 74.11; H, 7.39. Found: C, 74.14; H, 7.11.

Selective hydrolysis as described for **2b** yielded 78% of hydroxy-benzoate **7b**: Ir ($CHCl_3$): 3600,1710,1365, 1280,1195,1080 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 1.02 (s,3H), 1.18 - 2.27 (m,11H), 1.28 (s,3H), 2.32 - 2.51 (m,1H), 2.59 (dd,J=8Hz,J=13Hz,1H), 3.32 (dd,J=6Hz,J=13Hz,1H), 3.73 (dd,J=9Hz,J=12Hz, 1H), 3.65 - 4.02 (m,1H), 3.80 - 3.92 (m,1H), 3.94 (s,3H), 5.00 (t,J=9Hz,1H), 7.27 - 7.64 (m,6H), 8.01 - 8.12 (m,2H). Ms (70 eV, 170 °C): m/z (%) = 476 (M^+,9), 354 (50), 336 (11), 322 (25), 304 (15), 105 (100), 77 (25).
Ms Calcd for $C_{30}H_{36}O_5$: 476.2563. Found: 476.2563.

PCC-oxidation as described for **2c** yielded 91% of ketobenzoate **7c**: Ir ($CHCl_3$): 1710,1280,1265,1120 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.80 - 2.58 (m, 12H), 1.02 (s,3H), 1.28 (s,3H), 3.61 (d,J=16Hz,1H), 3.73 (d,J=16Hz,1H), 3.79 (dd,J=9Hz,J=12Hz,1H), 3.95 (s,3H), 4.10 - 4.21 (d,J=7Hz,1H), 5.02 (t,J=9Hz,1H), 7.38 - 7.66 (m,6H), 8.02 - 8.12 (m,2H). Ms (70 eV, 180 °C): m/z (%) = 474 (M^+,6), 352 (42), 320 (21), 302 (14), 211 (17), 193 (22), 134 (21), 105 (100), 77 (28).
Ms Calcd for $C_{30}H_{34}O_5$: 474.2406. Found: 474.2404.

Epoxidation as described for **6** gave rise to the following mixtures of epimeric epoxides (separation by flash chromatography).

7a → **8a** + **8b** (1.5 : 1) 84%. Ir ($CHCl_3$): 1715,1280,1250,1120 cm^{-1}. Ms (70 eV, 180 °C): m/z (%) = 534 (M^+,6), 502 (4), 474 (2), 442 (2), 412 (9), 397 (5), 380 (5), 352 (7), 320 (11), 105 (100), 77 (24).

8a: ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.88 - 2.60 (m,13H), 0.95 (s,3H), 1.12 (s,3H), 2.11 (s,3H), 2.66 (dd, J=8Hz,J=14Hz,1H), 3.21 (dd,J=5Hz,J=14Hz,1H), 3.83 - 3.98 (m,1H), 3.93 (s,3H), 4.82 - 4.97 (m,1H), 5.03 (t,J=9Hz,1H), 7.34 - 7.62 (m,5H), 7.70 (d,J=2Hz,1H), 8.00 - 8.09 (m,2H).

8b: ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.81 - 2.60 (m,13H), 1.02 (s,3H), 1.10 (s,3H), 2.10 (s,3H), 2.67 (dd, J=8Hz,J=13Hz,1H), 3.17 (dd,J=6Hz,J=13Hz,1H), 3.88 (t,J=10Hz,1H), 3.93 (s,3H), 4.65 - 4.80 (m,1H), 5.06 (t,J=9Hz,1H), 7.32 (dd,J=2Hz,J=8Hz,1H), 7.37 - 7.59 (m,4H), 7.70 (d,J=2Hz,1H), 7.99 - 8.10 (m,2H).

7c → **9a** + **9b** (1 : 1) 75%. Ir ($CHCl_3$): 1715,1275 cm^{-1}. Ms (70 eV, 170 °C): m/z (%) = 490 (M^+,10), 403 (6), 368 (10), 336 (14), 318 (6), 105 (100), 77 (29).

9a: ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.75 (dd,J=3Hz,J=7Hz,1H), 0.81 - 2.34 (m,11H), 1.00 (s,3H), 1.10 (s,3H), 2.41 - 2.62 (m,1H), 3.63 (d,J=14Hz,1H), 3.69 (d,J=14Hz,1H), 3.89 (dd,J=8Hz,J=12Hz,1H), 3.95 (s,3H), 5.04 (t, J=9Hz,1H), 7.37 - 7.63 (m,5H), 7.73 (d,J=2Hz,1H), 8.00 - 8.11 (m,2H).

9b: ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.70 - 2.58 (m,13H), 1.00 (s,3H), 1.13 (s,3H), 3.65 (s,2H), 3.81 (t,J=10Hz,1H), 3.96 (s,3H), 5.06 (t,J=9Hz,1H), 7.37 - 7.64 (m,5H), 7.70 (d,J=2Hz,1H), 8.00 - 8.12 (m,2H).

In the case of hydroxy compound **7b** α-epoxide **10a** was not isolated but rearranged under the reaction conditions to form ether **11**.

7b → **10a** + **11** (1 : 1.6) 99%. **10b**: Ir ($CHCl_3$): 3400,1710,1280,1120 cm^{-1}. ^1H Nmr (300 MHz, $CDCl_3$): δ = 0.80 - 1.89 (m,9H), 1.02 (s,3H), 1.08 (s,3H), 2.12 - 2.33 (m,2H), 2.40 - 2.55 (m,1H), 2.64 (dd,J=3Hz,J=13Hz, 1H), 2.98 (dd,J=6Hz,J=13Hz,1H), 3.09 (d,J=10Hz,1H), 3.75 - 3.88 (m,1H), 3.77 (dd,J=9Hz,J=12Hz,1H), 3.94 (s,3H), 5.08 (t,J=9Hz,1H), 7.40 - 7.60 (m,6H), 8.01 - 8.09 (m,2H). Ms (70 eV, 190 °C): m/z (%) = 492 (M^+,0.5), 474 (1), 415 (5), 370 (8), 352 (7), 338 (6), 320 (14), 302 (5), 105 (100), 77 (28).

Anal. Calcd for $C_{30}H_{36}O_6 \cdot 0.5\ H_2O$: C, 71.83; H, 7.43. Found: C, 72.29; H, 7.31.

11: Ir ($CHCl_3$): 3500,1710,1280,1120 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.59 - 0.43 (m,1H), 0.52 - 2.35 (m,10H), 0.98 (s,3H), 1.03 (s,3H), 2.42 - 2.64 (m,2H), 2.92 (d,J=14Hz,1H), 3.13 (dd,J=7Hz,J=14Hz,1H), 3.29 (t,J=10Hz,1H), 3.93 (s,3H), 4.16 - 4.31 (m,1H), 4.92 (dd,J=8Hz,J=9Hz,1H), 7.32 (dd,J=2Hz,J=8Hz,1H), 7.37 - 7.58 (m,4H), 7.61 (d,J=2Hz,1H), 7.98 - 8.06 (m,2H). Ms (70 eV), 170 °C): m/z (%) = 492 (M^+,6), 370 (23), 338 (9), 320 (14), 313 (36), 288 (29), 281 (31), 268 (15), 263 (14), 105 (100), 77 (31).

Ketone 13 by PCC oxidation of **11** as described for **2c**: Ir ($CHCl_3$): 1712,1280,1120 cm^{-1}. ^1H Nmr (300 MHz, $CDCl_3$): δ = 0.87 - 1.28 (m,2H), 1.04 (s,3H), 1.13 (s,3H), 1.43 - 1.60 (m,3H), 1.69 - 1.93 (m,3H), 2.13 - 2.25 (m,2H), 2.39 - 2.48 (m,1H), 2.49 - 2.64 (m,1H), 3.00 (d,J=14Hz,1H), 3.21 (dd,J=7Hz,J=14Hz,1H), 3.41

(dd,J=8Hz,J=12Hz,1H), 3.90 (s,3H), 4.32 - 4.42 (m,1H), 4.92 (t,J=9Hz,1H), 7.37 - 7.47 (m,3H), 7.51 - 7.61 (m,2H), 7.62 (d,J=2Hz,1H), 7.99 - 8.05 (m,2H). Ms (70 eV, 160 °C): m/z (%) = 490 (M^+,1), 462 (9), 402 (69), 344 (17), 340 (19), 312 (48), 280 (34), 105 (100).
Ms Calcd for $C_{30}H_{34}O_6$: 490.2355. Found: 490.2356.

Ketone 14 by rearrangement of **10b**: 20.5 mg (0.042 mmol) of epoxide **10b** was dissolved in 5 ml of dry dichloromethane and treated with 0.05 ml of boron trifluoride etherate. After 5 min at room temperature solid sodium bicarbonate and a few drops of methanol were added. The solution was filtered, evaporated, and the foamy residue purified by flash chromatography with petrol ether-methyl tert.butyl ether (1:3) to yield 14.6 mg (71%) of a colourless foam.
14: Ir ($CHCl_3$): 3600,3500,1715,1275,1120,1090 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.52 - 2.25 (m,12H), 0.86 (d,J=7Hz,3H), 1.02 (s,3H), 2.40 - 2.62 (m,1H), 2.69 (dd,J=9Hz,J=13Hz,1H),3.30 (dd,J=5Hz,J=13Hz, 1H), 3.61 (dd,J=8Hz,J=12Hz,1H), 3.86 - 4.02 (m,1H), 3.91 (s,3H), 4.96 (t,J=9Hz,1H), 7.48 - 7.63 (m,6H), 7.99 - 8.10 (m,2H). Ms (70 eV, 180 °C): m/z (%) = 492 (M^+,7), 460 (8), 370 (45), 338 (12), 320 (16), 257 (22), 105 (100), 77 (18).
Ms Calcd for $C_{30}H_{36}O_6$: 492.2512. Found: 492.2513.

Both hydroxy compounds **10b** as well as **11** gave rise to the corresponding acetates **15** and **12** respectively on standard acetylation conditions (pyridin, acetic acid anhydride, room temperature). Acetate **15** proved to be identical to **8b** described above.
Acetate 12: Ir ($CHCl_3$): 1715,1280,1120,1090 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.63 - 0.47 (m,1H), 0.55 (dd,J=10Hz,J=14Hz,1H), 0.69 - 1.52 (m,3H), 1.01 (s,6H), 1.66 - 1.95 (m,3H), 1.90 (s,3H), 2.03 - 2.30 (m,3H), 2.40 - 2.65 (m,1H), 2.95 (d,J=14Hz,1H), 3.13 (dd,J=7Hz,J=14Hz,1H), 3.50 (dd,J=9Hz,J=11Hz,1H), 3.98 (s,3H), 4.10 (dd,J=3Hz,J=12Hz,1H), 4.17 - 4.32 (m,1H), 4.85 (dd,J=8Hz,J=9Hz,1H), 7.33 (dd,J=2Hz, J=8Hz,1H), 7.38 - 7.59 (m,4H), 7.77 (d,J=2Hz,1H), 8.00 - 8.11 (m,2H). Ms (70 eV, 130 °C): m/z (%) = 534 (M^+,20), 412 (10), 352 (22), 330 (15), 320 (15), 105 (100), 77 (26).
Ms Calcd for $C_{32}H_{38}O_7$: 534.2618. Found: 534.2617.

Stereoselective epoxidation under Sharpless conditions, general procedure: 0.22 mmol of the corresponding hydroxy-olefin were treated with 0.022 mmol of $VO[acac]_2$ in 15 ml of dry benzene and heated. To the boiling solution 0.36 mmol of tert.butyl hydroperoxide was added and heating was continued for 20 min. The solution was diluted with methyl tert.butyl ether, washed with saturated aqueous sodium bisulfite solution,

sodium bicarbonate solution and brine. After evaporation of the solvent the residue was purified by flash chromatography with petrol ether-methyl tert.butyl ether (1:2).

16: 66% yield. Ir ($CHCl_3$): 3500,1710,1280,1120 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.76 - 2.62 (m,13H), 1.00 (s,3H), 1.10 (s,3H), 2.68 (dd,J=2.5Hz,J=13Hz,1H), 2.99 - 3.18 (m,1H), 3.05 (dd,J=5.5Hz,J=13Hz,1H), 3.76 - 3.96 (m,1H), 4.18 (dd,J=8Hz,J=12Hz,1H), 5.15 (t,J=9Hz,1H), 7.40 - 7.69 (m,6H), 8.01 - 8.11 (m,2H), 10.46 (s,1H). Ms (70 eV, 190 °C): m/z (%) = 462 (M^+,5), 444 (12), 416 (16), 340 (15), 322 (21), 304 (6), 105 (100), 77 (33).

Ms Calcd for $C_{29}H_{34}O_5$: 462.2406. Found: 462.2406.

Epoxidation of **17** which was obtained in a standard borohydride reduction (ethanol, 0 °C, 35 min) of **2a** gave rise to **18**: 66% yield. Ir ($CHCl_3$): 3500,1715,1280,1250,1120,1125 cm^{-1}. ^1H Nmr (300 MHz, $CDCl_3$): δ = 0.57 (d,J=10Hz,1H), 0.90 - 1.92 (m,9H), 0.99 (s,3H), 1.20 (s,3H), 2.09 - 2.21 (m,2H), 2.11 (s,3H), 2.45 - 2.60 (m, 1H), 2.72 (dd,J=7Hz,J=14Hz,1H), 2.84 - 2.99 (m,1H), 3.11 (dd,J=5Hz,J=14Hz,1H), 3.40 (t,J=10Hz,1H), 4.41 (d,J=12Hz,1H), 4.79 (d,J=12Hz,1H), 4.86 (m,1H), 5.07 (t,J=9Hz,1H), 7.22 - 7.30 (m,2H), 7.37 - 7.61 (m, 4H), 8.03 - 8.10 (m,2H). Ms (70 eV, 200 °C): m/z (%) = 506 (M^+,14), 488 (4), 446 (10), 428 (8), 415 (16), 324 (6), 306 (12), 105 (100), 77 (20).

Ms Calcd for $C_{31}H_{38}O_6$: 506.2668. Found: 506.2670.

Epoxidation of **7b** yielded 63% of epoxide **10b** identical to the compound described above.

Baeyer-Villiger oxidation of **7c**: 63 mg (0.13 mmol) of **7c** was dissolved in 5 ml of dry dichloromethane, 67 mg (0.39 mmol) of m-chloroperbenzoic acid, and 70 mg (0.83 mmol) of sodium bicarbonate were added and the mixture was stirred at room temperature for 10 days. It was added to water and extracted with dichloromethane. The dichloromethane solution was washed with saturated sodium bicarbonate solution and brine. After evaporation the reaction mixture was separated by flash chromatography. Petrol ether-methyl tert.butyl ether (1 : 1) and pure methyl tert.butyl ether provided **19** and **20**, respectively.

19 (28%): Ir ($CHCl_3$): 1715,1280 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.80 - 1.92 (m,8H), 1.03 (s,3H), 1.18 (s,3H), 2.05 - 2.56 (m,5H), 3.90 (t,J=10HZ,1H), 3.94 (s,3H), 4.99 (d,J=11Hz,1H), 5.05 (t,J=9Hz,1H), 5.22 (d,J=11Hz,1H), 7.49 - 7.63 (m,5H), 7.74 (d,J=2Hz,1H), 8.01 - 8.09 (m,2H). Ms (70 eV, 150 °C): m/z (%) = 506 (M^+,15), 384 (3), 352 (7), 334 (4), 286 (10), 268 (6), 254 (13), 105 (100), 77 (29).

Ms Calcd for $C_{30}H_{34}O_7$: 506.2305. Found 506.2306.

20 (29%): Ir ($CHCl_3$): 3600,1760,1710,1280 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$): δ = 0.92 (s,3H), 1.09 - 2.60 (m,12H), 1.17 (s,3H), 3.43 (d,J=9Hz,1H), 3.84 - 3.98 (m,1H), 3.90 (s,3H), 4.71 (s,2H), 5.25 (dd,J=7Hz,

J=8Hz,1H), 7.40 - 7.63 (m,5H), 7.68 (d,J=2Hz,1H), 7.99 - 8.08 (m,2H). Ms (70 eV, 220 °C): m/z (%) = 524 (M+,0.5), 402 (3), 384 (8), 370 (6), 352 ((19), 334 (7), 303 (10), 285 (7), 271 (9), 253 (21), 105 (100), 77 (27). Ms Calcd for $C_{23}H_{30}O_6$ (M-122 = benzoic acid): 402.2042. Found: 402.2039.

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