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DIASTEREO- AND ENANTIOSELECTIVE SYNTHESIS OF 1,2-DIOLS BY VANADIUM(II) PROMOTED PINACOL CROSS COUPLING.

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Abstract. The V(II) promoted pinacol cross coupling of a chiral aromatic aldehyde with chiral aliphatic aldehydes occurs to afford syn diols in up to 91·9 diastereoisomeric ratio and up to 84% enantiomeric excess The pinacol coupling of (S)-lactaldehyde and (R)-glyceraldehyde derivatives has also been studied and matching and mis-matching pairs have been identified The stereochemistry of the products was established by correlation The sense and degree of stereoselection is discussed.

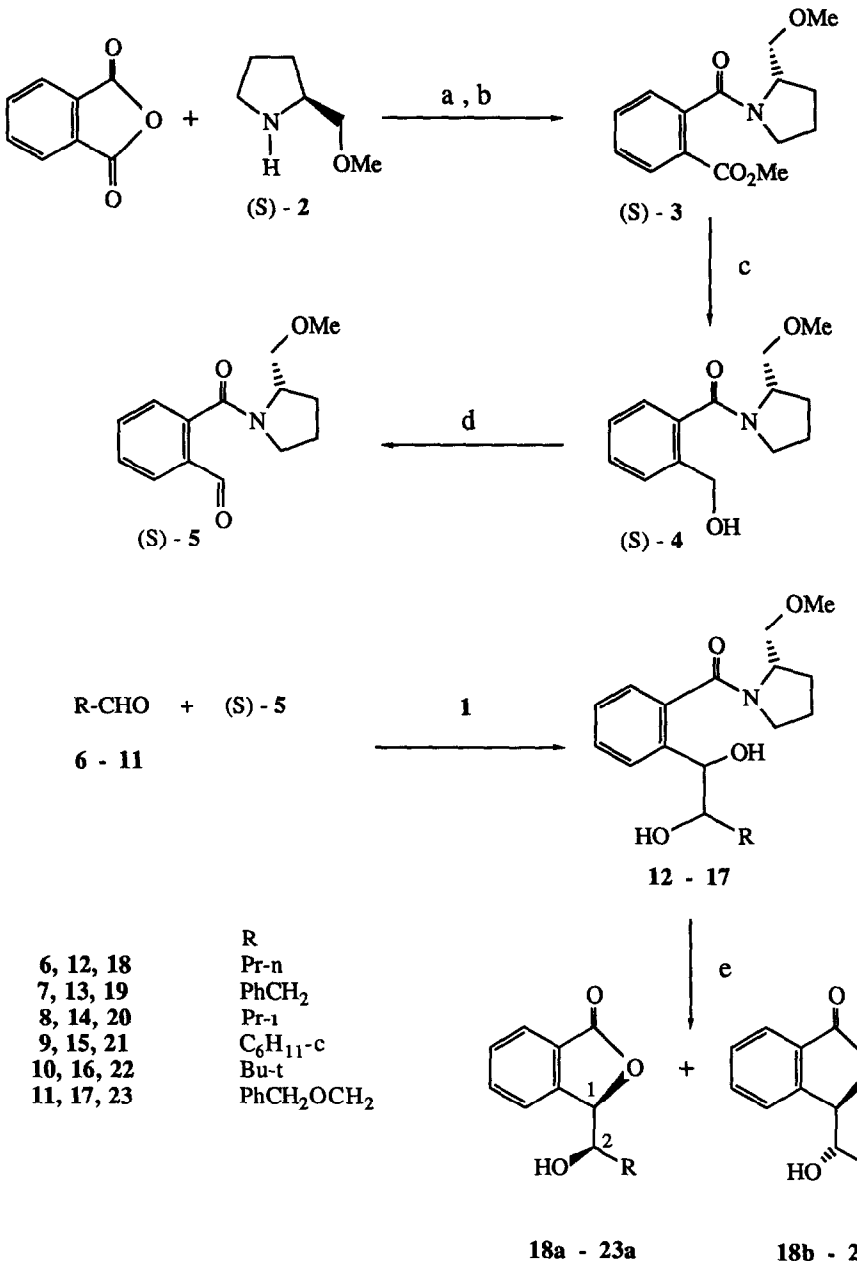
Very recently Pedersen and co-workers reported an efficient synthesis of 1,2 diols[1,2] that exploited an intermolecular pinacol coupling[3] of aldehydes promoted by the vanadium(II) complex **1** [4] In its most useful version this reaction allows to cross-couple, with high syn-stereoselectivity, an aliphatic aldehyde with a "ligand accelerated" aliphatic[1] or aromatic[2] aldehyde In the former case one of the two carbonyl compounds must bear in the β or γ position an amide group that is believed to favour the cross-coupling by intramolecular complexation.[1]

We reasoned that if the amide function is playing such an important role in this reaction, insertion of a chiral amide group could result in the control of the absolute stereochemistry of the products,thus making the pinacol condensation an attractive alternative to other enantioselective 1,2-diol syntheses.[5-8] Indeed, this method can be superior to osmylation[5] or to the epoxide formation/opening protocol[6] since it does not require control of alkene geometry, and can be more general than reduction or alkylation of α-alkoxy carbonyls[7] or than addition of α-alkoxy anions to aldehydes,[8] since these approaches demand enantiomerically enriched reagents

We here report[9] that the use of an amide chiral auxiliary leads to an highly enantioselective version of the pinacol coupling, thus greatly expanding the potentialities of Pedersen's diol synthesis.

Chiral amide (S)-**5** was easily prepared in 60-65% overall yield from phthalic anhydride and (S)-2-methoxymethylpyrrolidine **2**[10] via ester **3** and alcohol **4** as described in Scheme

Scheme 1



	R
6, 12, 18	Pr-n
7, 13, 19	$PhCH_2$
8, 14, 20	Pr-i
9, 15, 21	C_6H_{11}-c
10, 16, 22	Bu-t
11, 17, 23	$PhCH_2OCH_2$

Reagents a benzene, reflux, b CH_2N_2, THF, c $NaBH_4$, t-BuOH, MeOH, reflux, d PDC, CH_2Cl_2, e PTSA, THF

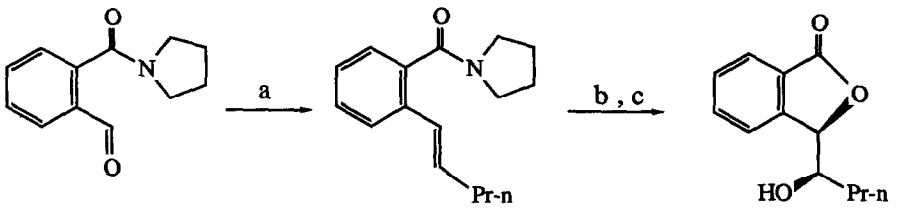
l.[11] Pinacol coupling of (S)-**5** with a series of aliphatic aldehydes[1,12] in the presence of **1**, followed by acidic work-up (see Experimental) afforded mixtures of diols **12-17** together with minor amounts of the corresponding lactones **18-23**. Since the conversion of **12-17** into **18-23** greatly simplifies the evaluation of the stereochemical outcome,[13] and in principle[14] allows the recovery of the chiral auxiliary, the crude products of the coupling reactions were directly converted into five membered lactones **18-23** ($\nu_{C=O}$ 1760-1770 cm^{-1}). Yields, diastereoisomeric ratios (d.r 's) of compounds **18a,b-23a,b** (as determined by 300 MHz ^{1}H-NMR spectroscopy), and enantiomeric excesses (e.e 's) of the major isomers[15] are collected in Table 1. The enantiomeric excesses were determined by LSR technique with Eu(hfc)$_3$ in conditions pre-established on racemic samples of **18-23**, synthesized by a sequence of reactions similar[16] to those depicted in Scheme 1, starting from phthalic anhydride and pyrrolidine, via the 2-formyl amide **24**.

The relative and absolute configuration was unambigously assigned in the case of compound **18a** by chemical correlation (Scheme 2) E-Alkene **25** was obtained from aldehyde **24** by Wittig reaction and isomer separation (Z/E ratio 66 34). Osmylation in Sharpless' stoichiometric conditions[5] (in the presence of acetyldihydroquinidine) and subsequent lactonization gave syn-**18a**, that showed the same ^{1}H-NMR spectrum and the same sign of rotation of the major isomer obtained by coupling of (S)-**5**. As crystallized[15] sample of **18a** (e.e.$\geqslant$96%) was deoxygenated to the known[17] (S)-3-butylphthalide **26**, a component of the essential oil of celery. Comparison of the rotation value of (S)-**26** obtained via the pinacol route with that reported by Mukaiyama[17] confirmed the enantiomeric purity ($\geqslant$96%) of crystallized **18a**.[18]

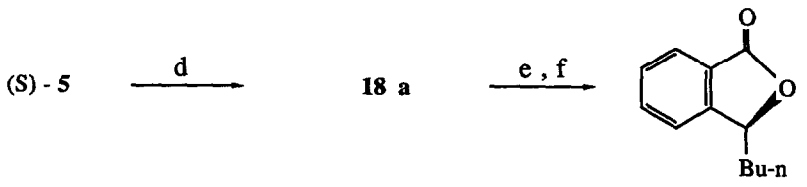
On this basis the (R,R) absolute configuration was assigned to the major enantiomer of **18a**.[18] Assignement of the (R,R)-syn stereochemistry to the major isomers **19a-23a** rests on the reasonable assumption that coupling of (S)-**5** with **6-11** should follow the same stereochemical course. This is in agreement with previous results[1], and is confirmed by comparison of ^{1}H chemical shift values of the Ar-CH-O and R-CH-O signals of compounds **18-23** (see Table 4).

The data reported in Table 1 require a few comments. The d r.'s of the reaction range from 4 1 to 9 1 and increase with increasing bulkiness of the aldehyde R residue, or when this group features an aromatic ring, very sterically demanding aldehyde **10** gave only syn **22**, albeit in low yield The e e.'s of major isomers range from 75% to 84%, being only slightly sensitive to aldehyde R group variation, aldehyde **10** being now a negative exception It must be noted that these e.e. values are rather high for these 1,6-inductions Finally, it is worth mentioning that the e e. of **18a** obtained by pinacol

Scheme 2.

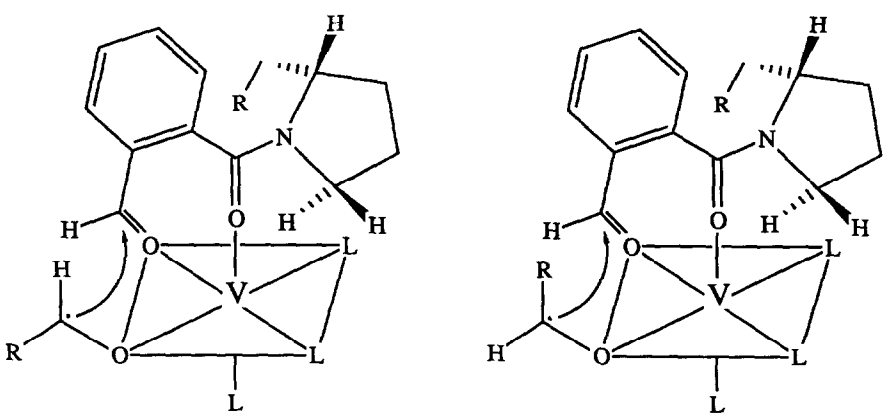


24 **25** **18 a**



(S) - **26**

Reagents. a n-$BuPPh_3Br$, BuLi, Et_2O, E/Z separation, b OsO_4, acetyldihydroquinidine, toluene, c PTSA, THF, d see Scheme 1, e· thiocarbonyldiimidazole, $ClCH_2CH_2Cl$, reflux, f Bu_3SnH, toluene, reflux



A **B**

Table 1. Stereoselective synthesis of lactones **18-23** by coupling of (S)-**5** with **6-11**.

Aldehyde	Product	T(°C)	Yield %[a]	d.r.[b]	e.e.[b,c]
6	**18**	-40	46	55 45	56
6	**18**	22	62	80 20	77
6	**18**	60	55	80·20	80
6	**18**	80	44	84 16	85
7	**19**	22	70	91 9	75
8	**20**	22	62	89 11	84
9	**21**	22	55	88 12	83
10	**22**	22	17	98 2	50
11	**23**	22	78	81 19	82

[a] Overall yield from **5**. [b] As determined by 300 MHz ^{1}H NMR spectroscopy. [c] Of the major isomer

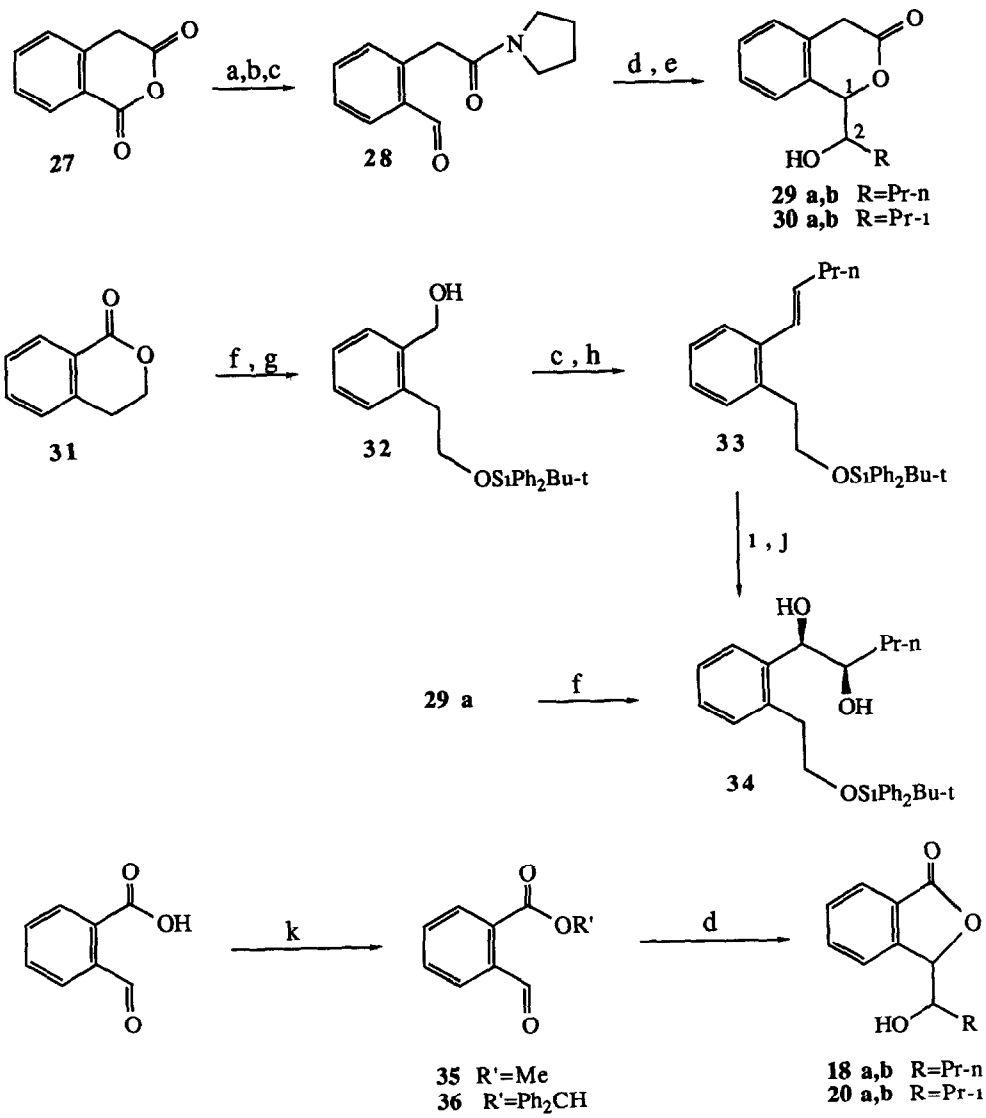
coupling (77%) is almost identical to that (80%) of the same compound obtained by enantioselective osmylation of E-**25**

Although the uncertainity about the mechanism of this pinacol coupling[1,3] makes highly speculative any razionalization of its stereochemical outcome, as a working hypothesis we propose models A and B for the formation of major and minor isomers, respectively.

In both A and B the vanadium is coordinated in a seven membered chelate to the aldehyde and amide oxygens of (S)-**5** and bound to the anion radical, deriving from the aliphatic aldehyde, which attacks the *si* face of **5** to minimize steric repulsion with the methoxymethyl group of the chiral auxiliary,[19] forced in the indicated conformation by the ligands at vanadium. The more favourable arrangement of the R residue and aromatic ring in A with respect to B accounts for the preferential formation of *syn*-isomers This is in agreement with the experimental results, since an increase of the steric requirements of the R residue leads to an increase of *syn* stereoselection.[20]

To gain further insight into the process, we studied the effect of a variation of the temperature of the coupling reaction on the extent of stereoselection. Therefore aldehyde (S)-**5** was reacted with **6** at -40°, 60° and 80°C (the last two reactions were carried out in 1,2-dichloroethane) (Table 1) The coupling at low temperature occurred

Scheme 3.



Reagents a pyrrolidine, benzene, reflux, b $NaBH_4$, t-BuOH, MeOH, reflux, c PDC, CH_2Cl_2, d **6** or **8**, **1**, CH_2Cl_2, e PTSA, THF, f $LiAlH_4$, Et_2O, g t-$BuPh_2SiCl$, imidazole, DMF, h n-$BuPPh_3Br$, BuLi, Et_2O, E / Z separation, i OsO_4

with a lower degree of diastereo- and enantioselectivity than that at room temperature, on the other hand a temperature increase was beneficial, although to a limited extent, for both d.r. and e.e values. These results seems to point out that rotation about the amide bond plays a relevant role in determining the stereochemical outcome. The importance of the geometry in the transition state, in particular of the distance of the amide group with respect to the formyl one, was apparent from the cross-coupling, in the presence of **1**, of homologous amide **28**, obtained from homophthalic anhydride **27**, (Scheme 3) with butanal and 2-methylpropanal to give, after lactonization, compounds **29a,b** and **30a,b** with diastereoselections comparable (84 16 and 87 13, respectively) but in yields (30% and 36%, respectively) by far inferior to those observed in the pinacol coupling of **5** (Table 2). The pinacol coupling is also in this case a syn selective process, as shown in the case of **29a** by chemical correlation with triol **34**, derived by osmylation of E-alkene **33** (Scheme 3) It must be noted that in the case of amide **28** homo-coupling of the aromatic aldehyde becomes competitive with cross coupling, and that the same is true in the case of esters **35, 36**. These were prepared (Scheme 3) via the cesium salt[21] of 2-formyl benzoic acid by reaction with iodomethane and chlorodiphenylmethane. Cross-coupling in the presence of **1** with butanal and 2-methylpropanal and subsequent lactonization afforded compounds **18a,b** and **20a,b** with excellent diastereoselectivities (Table 2) This seems to confirm that is indeed the amide or ester oxygen which is bound to vanadium in the transition state.

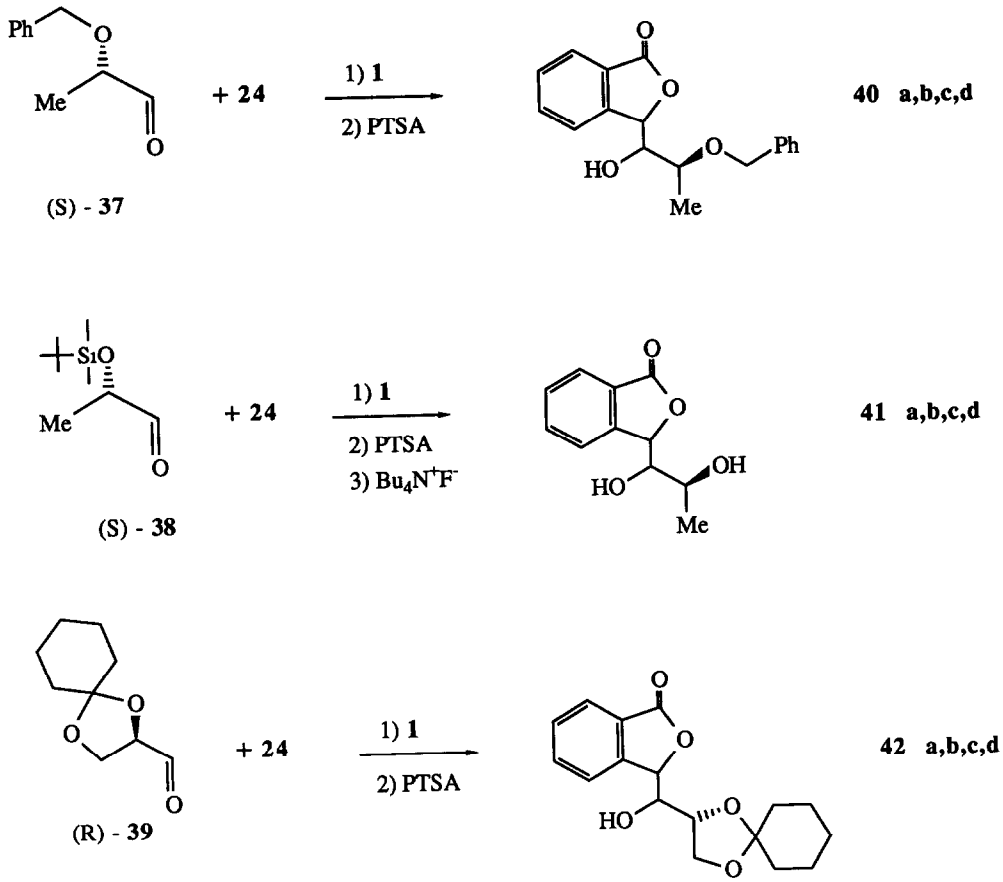
Having in hand a versatile and simple procedure for the diastereo- and enantioselective pinacol-type cross coupling, and in order to test the potentialities of our approach for

Table 2. Stereoselective coupling of **28, 35, 36** with aldehydes **6** and **8** at 22°C

Substrate	Aldehyde	Lactone	Yield %[a]	d r.[b]
28	**6**	**29a,b**	30	84 16
28	**8**	**30a,b**	36	87 13
35	**6**	**18a,b**	50	88 12
35	**8**	**20a,b**	54	97 3
36	**6**	**18a,b**	40	88 12
36	**8**	**20a,b**	20	98 2

[a] Overall yield from **28, 35, 36.** [b] As determined by 300 MHz ^{1}H NMR spectroscopy

Scheme 4.


Ph
O
Me
O
(S) - 37
+ 24
1) 1
2) PTSA
O
O
HO
O
Ph
Me
40 a,b,c,d
Si
O
Me
O
(S) - 38
+ 24
1) 1
2) PTSA
3) Bu4N+F-
O
O
HO
OH
Me
41 a,b,c,d
O
O
O
O
(R) - 39
+ 24
1) 1
2) PTSA
O
O
HO
O
O
42 a,b,c,d

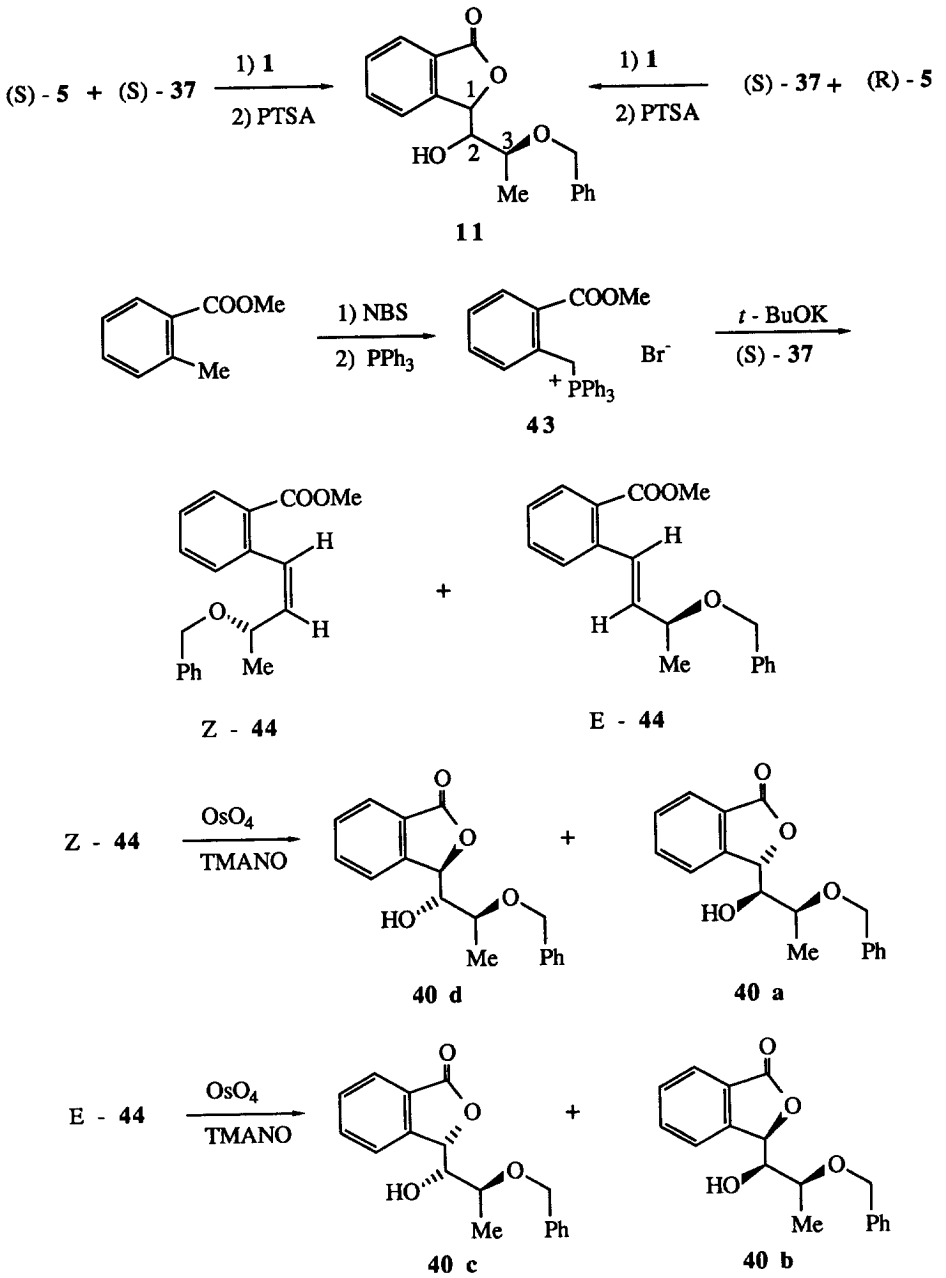
the synthesis of polyhydroxylated compounds, we decided to examine the reaction of (S)-**5** with chiral α- and α,β-alkoxy aldehydes.[22]

The chiral alkoxy aldehydes selected for our study were (S)-2-benzyloxypropanal **37**,[23] (S)-2-t-butyldimethylsilyloxy propanal **38**,[24] and (R)-cyclohexylidene glyceraldehyde **39**,[25] and the results were compared with those obtained (Table 1) in the case of benzyloxy acetaldehyde **11**,[26] an achiral equivalent of **37**. The behaviour of **11** in comparison with aliphatic aldehydes shows that the enantio- and diastereoselectivities are similar for alkoxy- and non-heterosubstituted aldehydes, and that the α-alkoxy group does not promote self coupling as a competitive process.[27]

The stereoselectivity of the reaction of **37-39** with **24** in the presence of **1** was then examined (Scheme 4 and Table 3). From (S)-**37** and **24** compound **40** was obtained (68% yield) as a 8 34 56 2 mixture of **a,b,c,d** diastereoisomers (elution order) as evaluated by ^{1}H-NMR spectroscopy (Table 4). The reaction of (S)-**38** gave a partly desilylated product (by NMR analysis of the crude lactone mixture) that was completely deprotected by reaction with $Bu_4N^+F^-$ to give (62% overall yield) **41a,b,c,d** as a 10 41 47 2 mixture of four isomers. The fact that aldehydes **37** and **38** that feature alkoxy groups of well differentiated chelating ability,[28,29] couple with **24** giving rise to similar product distribution suggests that the reaction does not involve an intramolecularly chelated alkoxy aldehyde. Finally the coupling of **24** and (R)-**39** afforded a 37 9 46 8 mixture of isomeric lactones **42a,b,c,d** in 69% yield.

With these results in hand we were ready to study the coupling between chiral partners (Table 3). To establish matching and mis-matching pairs,[30] compound (R)-**5** was prepared[4] starting from (R)-2-methoxymethylpyrrolidine. Reaction of (S)-**5** with (S)-**37** promoted by **1** (Scheme 5) gave a 28 51 19 2 mixture of lactones **40a,b,c,d** in 63% yield, while the combination of (R)-**5** and (S)-**37** afforded (66% yield) a 7 0 5 90 2 5 mixture of diastereoisomers, as the result of the coupling in which the configuration of the reagents co-operate in determining the stereochemical course of the reaction. The stereochemistry of the products was established by chemical correlation. Starting from methyl-2-methyl benzoate, benzylic bromination and reaction with triphenylphosphine gave phosphonium bromide **43**, that was condensed with (S)-**37** in Wittig conditions, to give a 66 34 mixture of alkenes Z-**44** and E-**44** (53% yield) that were separated by flash chromatography. Osmylation of Z-**44**, followed by spontaneous lactonization, gave a 70 30 mixture of products **40d** and **40a** in 73% yield, from E-**44**, **40c** and **40b** were obtained (70% yield) as a 66 34 mixture of isomers (Table 3). The configurational assignment resided on the stereochemical outcome[5] of the osmylation of chiral allyl ethers that occurs to give

Scheme 5.


(S) - 5 + (S) - 37
1) 1
2) PTSA
1) 1
2) PTSA
(S) - 37 + (R) - 5
11
COOMe
Me
1) NBS
2) PPh3
COOMe
Br-
+PPh3
43
t - BuOK
(S) - 37
COOMe
H
H
Ph
Me
Z - 44
+
COOMe
H
H
Me
Ph
E - 44
Z - 44
OsO4
TMANO
HO
Me
Ph
40 d
+
HO
Me
Ph
40 a
E - 44
OsO4
TMANO
HO
Me
Ph
40 c
+
HO
Me
Ph
40 b

an excess of the anti product. This configuration was therefore assigned at C-2/C-3 (see Scheme 5 for numbering) of **40d** and **40c** and the syn-configuration at C-2/C-3 of **40a** and **40b**. The known course of the osmylation reaction (C-1/C-2 anti-products from Z-alkenes, C-1/C-2 syn-products from E-alkenes) allows the complete attribution of configuration indicated in Scheme 5.

The reaction of (R)- and (S)-**5** with (S)-**37** requires a few comments. The combination of the mis-matching pair, (S)-**5** and (S)-**37**, depresses the diastereofacial selection on the aromatic aldehyde, i e the intrinsic tendency of the coupling reaction to give C-1/C-2 products of syn-stereochemistry (syn/anti ratio 70 30), and proceeds with low diastereofacial preference also on the alkoxy aldehyde (C-2/C-3 syn/anti ratio 79 21). On the other hand the matching pair reaction of (R)-**5** and (S)-**37** displays a 90 10 syn/anti selectivity at C-1/C-2, and a 92.5 7.5 anti/syn selectivity at C-2/C-3. Although these results require more experimental work to be fully rationalized, we think that the proposed model of stereoselection can be an useful working hypothesis to explain our results. In this line we postulate (see above) that the carboxyamide oxygen and the aldehyde oxygen of **5** bind to the vanadium species to give a seven membered chelate, and coordination (of the carbonyl oxygen) of **37** forms diastereoisomeric complexes. These differ in stereoselectivity as shown by the fact that (R)-**5** and (S)-**5** react with (S)-**37** with different sense and degree of stereoselection.

The reactions of Scheme 5 indicate that the matching combination of aldehyde configurations is (R)-**5** with (S)-**37**. On this basis we reacted (S)-**5** with (R)-**39** as shown in Scheme 6. Indeed, this reaction was highly stereoselective[31] affording (66% yield) a 8 2 87 3 mixture of the four isomers of lactone **42**, the configuration of which was demonstrated following the alkene osmylation protocol described above (Scheme 6 and Table 3). Reaction of **43** with (R)-**39** gave the two isomeric alkenes Z-**45** and E-**45** (51% yield) in 75 25 ratio Osmylation of the Z-product afforded lactones **42a** and **42d** (80% yield) in a 65 35 ratio, from E-**45** a 58 42 mixture of **42b** and **42c** was obtained in 67% yield. Following the above described reasoning, the structures reported in Scheme 6 were assigned to these lactones Therefore, for the coupling reaction between (S)-**5** and (R)-**39** the syn selectivity at C-1/C-2 is good (89 11 syn/anti ratio), as it is the diastereofacial selection on **39**, but, differently from the case of (S)-**37**, a preference for the C-2/C-3 syn product was observed (syn/anti ratio 90 10). By comparing the results of the reaction of Scheme 5 and 6 it is particularly relevant the very high alkoxy aldehyde diastereoface selection featured by the coupling reaction leading to C-1/C-2 syn configurated products (**40c**: **40b** 99 1, **42c**: **42b** = 98 2). This makes this reaction a

Scheme 6.

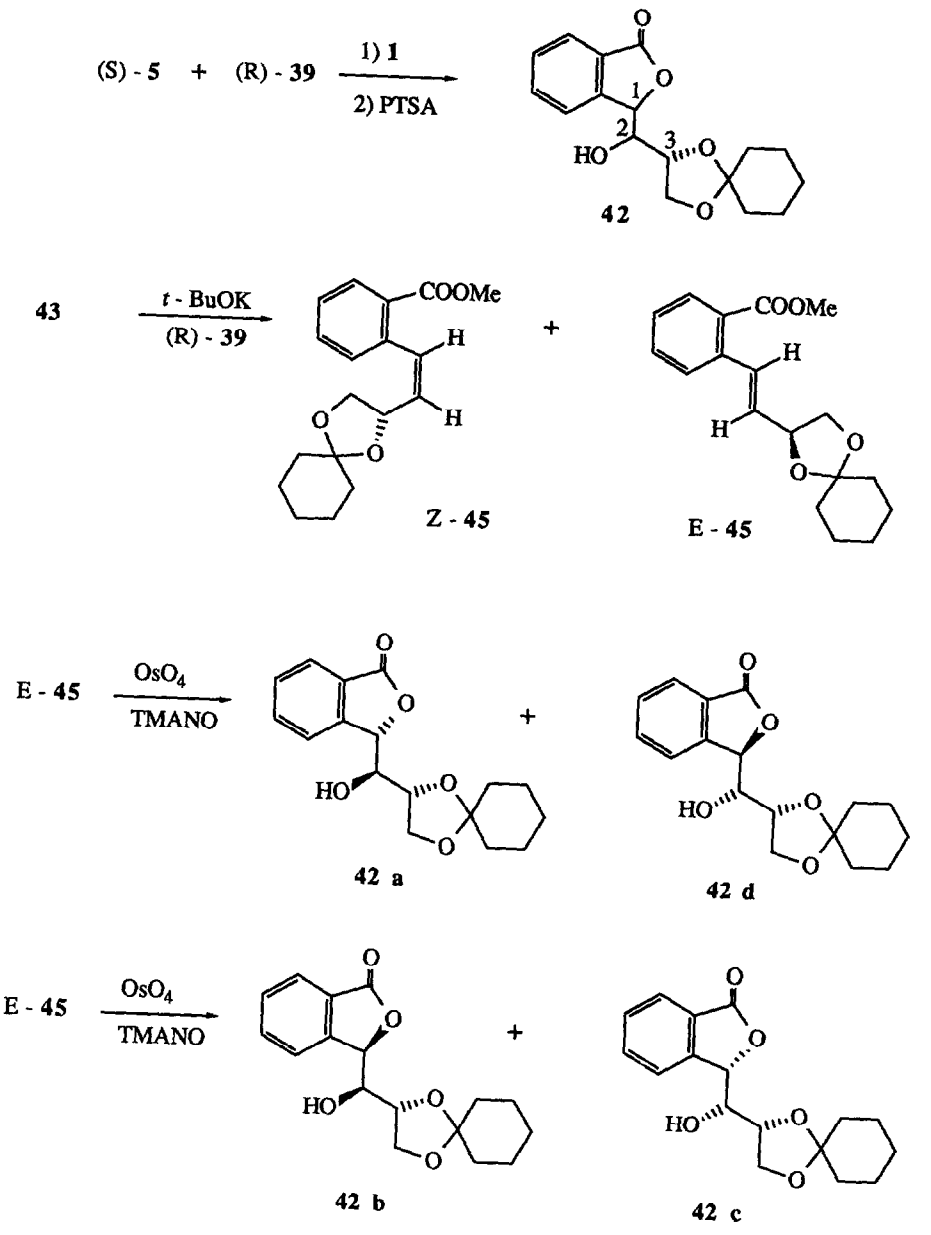

(S) - 5 + (R) - 39
1) 1
2) PTSA
42
43
t - BuOK
(R) - 39
COOMe
H
Z - 45
E - 45
E - 45
OsO4
TMANO
HO
42 a
42 d
E - 45
OsO4
TMANO
42 b
42 c

Table 3 Stereoselective synthesis of lactones **40-42** by coupling of **5** and **24** with **37-39** and by osmylation of **44** and **45**.

Reagents	Product	Yield %[a]	Diastereoisomeric ratio[b]			
			a	**b**	**c**	**d**
24 / (S)-**37**	**40**	68	8	34	56	2
24 / (S)-**38**	**41**	62[c]	10	41	47	2
24 / (R)-**39**	**42**	69	37	9	46	8
(S)-**5** / (S)-**37**	**40**	63	28	51	19	2
(R)-**5** / (S)-**37**	**40**	66	7	0.5	90	2.5
(S)-**5** / (R)-**39**	**42**	66	8	2	87	3
Z-**44** / OsO_4	**40**	73	30	-	-	70
E-**44** / OsO_4	**40**	70	-	34	66	-
Z-**45** / OsO_4	**42**	80	65	-	-	35
E-**45** / OsO_4	**42**	67	-	58	42	-

[a]Overall yield of coupling and lactonization. [b]As determined by 300 MHz ^{1}H-NMR spectroscopy on crude products or enriched mixtures of isomers. [c]Overall yield of coupling, lactonization, and desilylation reactions

competitive process with respect to osmylation of E-allyl ethers that leads to the same compounds.

In conclusion we have found that the V(II) promoted pinacol coupling of aldehyde **5** with achiral aliphatic aldehydes and chiral alkoxy aldehydes represents a highly stereoselective entry to polyhydroxylated molecules Extension of this methodology to other chiral aldehydes is currently underway in our laboratories.[32]

Acknowledgments. Partial financial support by MURST-Roma is gratefully acknowledged

Table 4. Relevant ^{1}H -NMR data for lactones **18-23,29,30,40-42.**

Compound	HC-1	HC-2	HC-3	J_{1-2}	J_{2-3}
18a	5.41	4.01	-[a]	3.8	5.3/9.0
18b	5.39	3.93	-[a]	4 8	3 3/9.0
19a	5 45	4.29	2 97	3.0	6 3/9.0
19b	5 35	3.96	3 00	7.3	3 6/9.1
20a	5 58	3.62	2 10	2.9	7 2
20b	5 43	3 59	2 15	6 6	6 2
21a	5.61	3 65	1 93	3.0	6 0
21b	5.48	3 62	1.93	6.4	6.4
22a	5.66	3 67	-	0.0	-
22b	5.35	3.28	-	8.4	-
23a	5.61	4.27	3 67	3 1	5.5/8.6
23b	5.43	3 80	3 80	7 3	-[a] -[a]
29a	5.26	3 96	-[a]	3 0	5 3/9 0
29b	5 28	4.10	-[a]	4 0	3 3/9.0
30a	5 46	3.53	2.05	2 6	7 6
30b	5.40	3 70	1 86	5.0	6 2
40a	5 43	3.87	3 93	7.9	4 7
40b	5 56	3.95	3.82	3 2	6 4
40c	5 93	3.87	3.87	0 0	-[a]
40d	5 40	3 93	4 13	9 5	1.5
41a	5.49	3 78	4 15	7.0	6 0
41b	5.81	3 86	4.08	2.0	7 0
41c	5.07	4.21	4.39	2 0	5 6
41d	5 55	3 76	4.11	3 7	3 0
42a	5 58	4 14	4 23	4.8	7 0
42b	5.54	4 49	4.20	2 5	-[a]
42c	5.76	3.99	4.31	0 0	7.9
42d	5.33	3.43	4 53	7.0	-[a]

[a]Undetermined because of peak overlap.

Experimental

NMR spectra were recorded on a Bruker WP-80 or a Varian XL-300 instrument using $CDCl_3$ as solvent, chemical shifts are in ppm downfield from TMS IR spectra were recorded on a Perkin Elmer 377 instrument Elemental analyses were obtained on a Perkin Elmer 240 instrument. Optical rotations were measured on a Perkin Elmer 241 polarimeter. THF and Et_2O were distilled from $LiAlH_4$, benzene from sodium; CH_2Cl_2 and DMF from CaH_2, MeOH from Mg turnings. Dry solvent were stored under Argon over molecular sieves. Aldehydes **11**, **37-39** were prepared according to literature procedures.[23-26] (R)- and (S)-2-methoxymethyl pyrrolidine were prepared[10] from commercially available (R)- and (S)-prolinol.

General Procedure for the Preparation of Aldehydes 5, 24, and **28.**

Products **5** and **24** were prepared in four steps from phthalic anhydride via addition of amine, esterification, reduction to the alcohol and oxidation to the aldehyde. Synthesis of the esters To a suspension of phthalic anhydride (14.8 g, 100 mmol) in dry benzene (250 ml), a solution of the amine (100 mmol) in benzene (50 ml) was added dropwise, and the mixture refluxed overnight. The solvent was evaporated and the crude acid dissolved in THF (100 ml) and treated with an ethereal solution of diazomethane at 0°C to give the methyl esters in 85-92% yield after filtration on a short column of silica gel. The products were used without further purification. Reduction to the alcohols[33] To a refluxing mixture of ester (10 mmol) and $NaBH_4$ (0.95 g, 25 mmol) in t-BuOH (36 ml), MeOH (7 2 ml) was added dropwise in 0 5 ml portions over a period of 1h. After 1h at reflux, H_2O (10 ml) was added and the cooled mixture was extracted several times with CH_2Cl_2 Evaporation of the solvent gave the crude alcohols (83-90% yield) that could be used as such. Oxidation to the aldehydes A suspension of the alcohol (10 mmol), pyridinium dichromate (3 76 g, 10 mmol), and pulverized 4A molecular sieves (1.0 g) in dry CH_2Cl_2 (20 ml) was stirred at room temperature for 24 h The mixture was filtered through a celite cake and the solvent evaporated to give a residue that was purified by flash chromatography with a 98 2 diethylether methanol mixture as eluant. Aldehyde (S)-**5** was obtained in 87% yield as a thick oil, it had $[\alpha]_D^{22}$+ 113.7 (c 1 2, $CHCl_3$). Aldehyde (R)-**5** was obtained in 85% yield, it had $[\alpha]_D^{22}$ -111 7 (c 0 48, $CHCl_3$) Found C, 67 88, H, 6 99, N, 5 60. $C_{14}H_{17}NO_3$ requires C, 68.00, H, 6 93, N, 5 66 ^{1}H-NMR ∂ 9.95 (s, 1H), 7 20-7 90 (m, 4H), 4 35-4 55 (m, 1H), 3 65-4.00 (m, 2H), 3 30 (s, 3H), 2.95-3.20 (m, 2H), 1.80-2.10 (m, 4H) IR ν 2940, 1690, 1630, 1590, 1380, 1080, 730 cm^{-1}. Aldehyde **24** was obtained in 89% yield as an oil that solidifies upon standing in the freezer. Found C, 71.03, H, 6 55, N, 6 81 $C_{12}H_{13}NO_2$ requires C, 70.91, H, 6.45; N, 6 89 ^{1}H-NMR ∂ 9.95

(s, 1H), 7.20-7.90 (m, 4H), 3 30-3.70 (m, 4H), 1.80-2.10 (m, 4H) IR ν 2945, 1690, 1620, 1590, 1385, 1080, 730 cm^{-1}. Aldehyde **28** was prepared following the same procedure described for **24** starting from homophthalic anhydride. A 85 15 mixture of regioisomeric esters was obtained (63% yield) in favour of the desired benzoic acid derivative Reduction (71%) and oxidation (85%) gave aldehyde **28** as a thick oil. Found C, 72.01, H, 7.00, N, 6.39. $C_{13}H_{15}NO_2$ requires C, 71.86; H, 6.96, N, 6.45 ^{1}H-NMR δ 10.05 (s, 1H), 7 20-7.90 (m, 4H), 3 95 (s, 2H), 3.35-3.60 (m, 4H), 1.75-2.10 (m, 4H). IR ν 2940, 1690, 1650, 1400, 1080, 730 cm^{-1}.

General Procedure for the Preparation of Aldehydes 35, 36. The cesium salt[21] of 2-formylbenzoic acid (5 mmol) was dissolved in dry DMF (10 ml) and alkylated with MeI (0.622 ml, 10 mmol) or Ph_2CHCl (2 02 g, 10 mmol) at RT for 15 h. The reaction mixture was poured into water and extracted several times with diethylether. The product was purified by flash chromatography with a 70 30 hexanes diethylether mixture as eluant Methyl-2-formylbenzoate **35**, a known compound,[34] was obtained in 75% yield. Diphenylmethyl-2-formylbenzoate, **36**, was obtained in 66% yield as a white solid, m p 70-71°C Found· C, 79.81, H, 5.07. $C_{21}H_{16}O_3$ requires C, 79 73, H, 5.10. ^{1}H-NMR δ 10 05 (s, 1H), 7 00-7.90 (m, 14H), 6 05 (s, 1H). IR ν 3100, 3000, 2960, 1720, 1690, 1590, 1430, 1270, 1130, 1070, 730 cm^{-1}

General Procedure for the Coupling Reaction. To a stirred solution of $VCl_3(THF)_3$[4] (0 746 g, 2 mmol) in dry CH_2Cl_2 (5 ml), Zn dust (0.078 g, 1 2 mmol) was added. After 15 min. stirring at room temperature the solution colour changed from dark red to green and the aldehyde (1 mmol) in CH_2Cl_2 (2 ml) was added dropwise. After 10 min. stirring at room temperature, the aromatic aldehyde (1 mmol) in CH_2Cl_2 (2 ml) was added over a 10 min period Stirring was continued overnight for aliphatic aldehydes and 0.5-2 h for alkoxy aldehydes, and then the reaction was quenched by addition of 10ml of a 1N aqueous solution of HCl. When the organic layer became clear and colourless, the two phases were separated and the aqueous phase was extracted twice with CH_2Cl_2, the combined organic phases were washed with an aqueous solution of $NaHCO_3$, dried, and evaporated to give the crude diol This was dissolved in THF (10 ml) and to this solution PTSA (0.190 g, 1 mmol) was added, and the mixture stirred overnight at room temperature Solid $NaHCO_3$ was then added, the mixture was filtered and the solvent concentrated to give the crude lactones, that were purified by flash chromatography with hexanes diethylether mixtures as eluant (with pure diethylether in the case of compound **41**) Yields and isomer ratios are collected in Table 1-3, relevant ^{1}H-NMR data in Table 4.

Compound **18** Found C, 69 84, H, 6 80. $C_{12}H_{14}O_3$ requires C, 69 88; H, 6.84 **18a**,

crystallized from $(i\text{-Pr})_2O$, had m.p. 106-107°C, $[\alpha]_D^{22}$-40.0 (c 1 2, $CHCl_3$), e.e.$\geqslant$96%. IR ν 3400, 3050, 2960, 1765, 1260, 740 cm^{-1}.

Compound **19**. Found· C, 75.66, H, 5.47 $C_{16}H_{14}O_3$ requires C, 75.57, H, 5 55 **19a**, obtained from the mother liquor of the crystallization of **19a,b** from a $(i\text{-Pr})_2O$ AcOEt 4 1 mixture, had m.p 124°C, $[\alpha]_D^{22}$-55 0 (c 1.1, $CHCl_3$), e.e $\geqslant$96%. IR ν 3400, 3050, 2960, 1765, 1260, 730 cm^{-1}

Compound **20**. Found C, 69.91, H, 6 90 $C_{12}H_{14}O_3$ requires C, 69.88, H, 6.84. **20a** had m p. 140-141°C, $[\alpha]_D^{22}$-60.3 (c 0 5, $CHCl_3$), e.e. 84% IR ν 3400, 3050, 2955, 1760, 1250, 730 cm^{-1}

Compound **21**. Found C, 73.03, H, 7 41. $C_{15}H_{18}O_3$ requires C, 73 14, H, 7.37 **21a**, crystallized from $(i\text{-Pr})_2O$ had m p 134°C, $[\alpha]_D^{22}$-53.7 (c 0 8, $CHCl_3$), e.e $\geqslant$96%. IR ν 3400, 3040, 2960, 1765, 1250, 740 cm^{-1}

Compound **22**. Found C, 71 00, H, 7 38. $C_{13}H_{16}O_3$ requires C, 70 89, H, 7 32. **22a**, had m p. 143°C, $[\alpha]_D^{22}$-51 0 (c 0 2, $CHCl_3$), e e. 50%. IR ν 3400, 3040, 2960, 1760, 1260, 740 cm^{-1}

Compound **23**. Found C, 71 89, H, 5.73 $C_{17}H_{16}O_4$ requires C, 71 82, H, 5.67 The two diastereoisomers were not separated the mixture was a thick oil IR ν 3400, 3040, 2960, 1760, 1250, 1150, 1070, 740 cm^{-1}

Compound **29** Found C, 70 97, H, 7 27 $C_{13}H_{16}O_3$ requires C, 70 89, H, 7 32 The two diastereoisomers were not separated The mixture was an oil that solidifies in the freezer IR ν 3400, 3040, 2960, 1745, 1250, 740 cm^{-1}

Compound **30** Found C, 70 99, H, 7.37. $C_{13}H_{16}O_3$ requires C, 70 89, H, 7.32. The two diastereoisomers were not separated The mixture was a low melting material IR ν 3400, 3040, 2965, 1740, 1250, 740 cm^{-1}

In the case of lactones **40-42** the products were obtained as mixture of diastereoisomers. They were thick colourless oils

Compound **40** Found C, 72 40, H, 6.13 $C_{18}H_{18}O_4$ requires C, 72.47, H, 6 08 IR ν 3400, 3040, 2940, 1760, 1600, 1440, 1250, 735 cm^{-1}

Compound **41** Found C, 63 41, H, 5 78 $C_{11}H_{12}O_4$ requires C, 63.45, H, 5 81 IR ν 3300, 3040, 2950, 1755, 1440, 1250, 735 cm^{-1}

Compound **42**. Found C, 66 94, H, 6 66 $C_{17}H_{20}O_5$ requires C, 67 09, H, 6 62. IR ν 3400, 3050, 2920, 1755, 1595, 1450, 1260, 1040, 730 cm^{-1}

Synthesis of alkene 25. To a suspension of butyltriphenyl phosphonium bromide (0.8 g, 2 mmol) in dry diethylether (20 ml) a 1M solution of n-BuLi in hexane (2 ml, 2 mmol) was added dropwise and the mixture stirred for 4 h at RT. Aldehyde **24** (0 406 g, 2 mmol) in

diethylether (20 ml) was then added, and the mixture stirred at RT for 15 h. The reaction was quenched by addition of a dilute HCl solution, the organic phase was separated, washed with water, dried and concentrated to give the crude product that was purified by flash chromatography with a hexanes ethylacetate 30.70 mixture as eluant. The required E-alkene (J CH=CH 15.8 Hz) was obtained as an oil in 21% yield (along with a 43% yield of Z-alkene). Found C, 79.05, H, 8.63, N, 5.70 $C_{16}H_{21}NO$ requires C, 78.97, H, 8 70, N, 5.76. IR ν 2940, 2860, 1630, 1610, 1415, 1380, 1080, 730 cm^{-1}.

General Procedure for the Synthesis of Alkenes 44 and 45. A stirred solution of methyl-2-bromomethylbenzoate[35] (2.29 g, 10 mmol) and triphenylphosphine (2.62 g, 10 mmol) in toluene (100 ml) was refluxed for 15h. A white precipitate was formed, that was filtered, washed with toluene and hexane, dried under vacuum and used without further purification To a suspension of the phosphonium salt (1 0 g, 2.43 mmol) in dry benzene (30 ml) cooled at 0°C, potassium t-butoxide (0.272 g, 2 43 mmol) was added in one portion. Cooling was removed and the mixture stirred at room temperature for 1h To the orange solution, a benzene (10 ml) solution of the aldehyde (2 5 mmol) was added dropwise, and the mixture stirred for 4 h. A saturated aqueous solution of NH_4Cl was then added, the layers were separated, and the aqueous phase was extracted three times with diethylether. Evaporation of the solvent gave the crude olefins that were purified by flash chromatography with a 80 20 hexanes diethylether mixture as eluant The products were oils. Compound **44** 53% yield. Found C, 76 91, H, 6.73. $C_{19}H_{20}O_3$ requires C, 77 00, H, 6.80 IR ν 3040, 2940, 1710, 1610, 1415, 1080, 730 cm^{-1} E-isomer δ 7.15-7 95 (m, 10H), 6.05 (dd, 1H, J = 16.0, 8 0 Hz), 4 40-4.80 (AB system, 2H), 4 00-4.35 (m, 1H), 3.90 (s, 3H), 1.35 (d, 3H, J= 7 0 Hz), $[\alpha]_D^{22}$-13.7 (c 0 3, $CHCl_3$) Z-isomer δ 7 00-8.00 (m, 10H), 5.65 (dd, 1H, J= 11 4, 9.3 Hz), 4 10-4 50 (AB system, 2H), 3.95- 4.10 (m, 1H), 3 85 (s, 3H), 1.35 (d, 3H, J= 7 0 Hz), $[\alpha]_D^{22}$-18.0 (c 0 5, $CHCl_3$) Compound **45** 51% yield Found C, 71 57, H, 7 27. $C_{18}H_{22}O_4$ requires C, 71.50, H, 7.33 IR ν 3040, 2950, 1710, 1610, 1410, 1080, 740 cm^{-1} E-isomer δ 7 10-7 95 (m, 5H), 6 05 (dd, 1H, J= 15 8, 8.0 Hz), 4.60-4 85 (m, 1H), 3 60-4 30 (m, 2H), 3.90 (s, 3H), 1.30-1 80 (m, 10H), $[\alpha]_D^{22}$+14.3 (c 1.2, $CHCl_3$). Z-isomer δ 6.95-7 90 (m, 5H), 5 60 (dd, 1H, J= 11.2, 9 0 Hz), 4.35-4 70 (m 1H), 3.30-4.00 (m, 2H), 3 80 (s, 3H), 1.25-1 70 (m, 10H), $[\alpha]_D^{22}$+19 6 (c 0.5, $CHCl_3$).

Synthesis of 18a by osmylation of 25.[5] To a stirred solution of **25** (0 061 g, 0 25 mmol) and acetyldihydroquinidine (0.120 g, 0 33 mmol) in toluene (5 ml) cooled at 0°C, a 0.2 M solution of OsO_4 in toluene (1.65 ml, 0 33 mmol) was added dropwise. The mixture was stirred at RT for 22h. The reaction was quenched by addition of an aqueous solution of $NaHSO_3$, the mixture filtered, and the aqueous phase extracted twice with dichloromethane,

dried, and evaporated to give the product that was converted, as described above into lactone **18a**, $[\alpha]_D^{22}$-32.0 (c 1.3, $CHCl_3$), e.e. 80%

Osmylation of 44 and 45. To a stirred solution of alkene (1 mmol) and trimethylamine-N-oxide dihydrate (TMANO 0.222 g, 2 mmol) in THF (9 ml) and H_2O (1 ml), a 0.01 M solution of OsO_4 in t-BuOH (2 ml) was added and the mixture stirred at room temperature for 12-15 h. A saturated aqueous solution of $NaHSO_3$ was then added and, after 30 min stirring, diethylether was added and the two phases separated. The aqueous layer was extracted twice with diethylether and the combined organic phases dried and concentrated to give the crude lactones, **40** and **42** that were purified by flash chromatogrpahy (see above)

Synthesis of (S)-26 from enantiomerically pure 18a. To a crystallized sample of **18a** (0.144 g, 0.7 mmol) dissolved in 1,2-dichloroethane (2 ml), was added thiocarbonyl diimidazole (0 178 g, 1.4 mmol) in 1,2-dichloroethane (0.5 ml). The reaction was refluxed for 4h and concentrated in vacuum. The residue was dissolved in dichloromethane, the organic phase was washed with 1N aqueous HCl solution, than with a 5% aqueous $NaHCO_3$ solution, and with water The product was purified by flash chromatography with a 60 40 hexane ethylacetate mixture as eluant The yield was 53%. A toluene (2 ml) solution of this product was slowly added to a refluxing solution of Bu_3SnH (0 151 ml, 0.57 mmol) in degassed toluene (10 ml). The solution was refluxed for 5h. Evaporation of the solvent gave the crude product, that was purified by flash chromatography with a 70 30 hexanes diethylether mixture as eluant, to give (S)-3-butylphthalide **26** in 84% yield. This product had $[\alpha]_D^{22}$-66 4 (c 1, $CHCl_3$), lit.[17] $[\alpha]_D^{22}$-50.0 ($CHCl_3$), for a sample of 88% e.e.

Synthesis of 34 and chemical correlation with 29a. Triol **34** was obtained in five steps from isochromanone **31**[36] by reduction ($LiAlH_4$, Et_2O, RT, 1h) protection (t-$BuPh_2SiCl$, imidazole, DMF, RT, 15h), and oxidation (PDC, CH_2Cl_2, RT, 15 h) of the crude sylilation product **32**, to give the corresponding aromatic aldehyde This was isolated in 57% overall yield from **31** as an oil, and transformed into alkene **33** as described above for the synthesis of **25**.

Compound **33** was obtained as a 60 40 mixture of Z and E isomers in 65% yield Found C, 81.41, H, 8.37 $C_{29}H_{36}OSi$ requires C, 81.25, H, 8.46 IR ν2940, 2860, 1610, 1410, 730 cm^{-1}. E-**33** δ 7.05-7.65 (m, 14H), 6 57 (d, 1H, J 15.8 Hz), 6 00-6 05 (m, 1H), 3 70-3.85 (m, 2H), 3 01 (t, 2H), 2 07-2 15 (m, 2H), 1.40-1 50 (m, 2H); 1.00 (s, 9H), 0.95 (t, 3H) Catalytic osmylation of **33** (see above for the synthesis of **40** from **44**) and deprotection (Bu_4NF, THF) gave triol **34** (76% overall yield from **33**). This product (a waxeous solid)

was obtained from the major isomer (**29a**) of the pinacol coupling of **28** with **6** in the presence of **1** (Table 2) by $LiAlH_4$ reduction (93% yield) in refluxing diethylether, after flash chromatography with a 95.5 diethylether methanol mixture as eluant. Found C, 69.52, H, 9.04. $C_{13}H_{20}O_3$ requires C, 69.61, H, 8 99. Relevant ^{1}H-NMR data δ 4 71 (d, 1H, J 7.5 Hz), 3.80-3 96 (m, 3H), 2.90-3.05 (ddd, 2H, J 7.5, 5.6, 5 6 Hz). IR ν 3300, 2940, 2860, 1250, 1080, 740 cm^{-1}.

References and notes.

1) Freudenberger, J.H., Konradi, A W , Pedersen, S F. J. Am. Chem. Soc. **1989**, 111, 8014.

2) Takahara, P.M , Freudenberger, J H., Konradi, A.W., Pedersen, S F Tetrahedron Lett. **1989**, 7177, Park, J., Pedersen, S.F. J. Org. Chem. **1990**, 55, 5924.

3) Reviews McMurry, J.E. Chem. Rev. **1989**, 89, 1513, Pons, J.M , Santelli, M. Tetrahedron **1988**, 44, 4295.

4) Cotton, F.A., Duraj, S.A , Roth, W.J. Inorg. Chem. **1985**, 24, 913, and references therein

5) Review Nakajima, M., Tomioka, K , Koga, K. J Synth Org. Chem. Jpn. **1989**, 47, 878. Recent reports Corey, E J , Da Silva Jardine, P , Virgil, S., Yuen, P.-W., Connell, R.D. J. Am. Chem. Soc. **1989**, 111, 9243, Oishi, T , Hirama, M J Org Chem. **1989**, 54, 5834, Tomioka, K., Nakajima, M , Koga, K Tetrahedron Lett **1990**, 1741, Kuong, H -L., Sorato, C.; Ogino, Y., Chen, H., Sharpless, K B. Tetrahedron Lett. **1990**, 2999, Kim, B M., Sharpless, K.B. Tetrahedron Lett. **1990**, 3003.

6) Beherens, C H., Ko, S Y , Sharpless, K.B , Walker, F J J Org Chem **1985**, 50, 5687, and references therein.

7) Eliel, E.L Asymmetric Synthesis **1983**, vol 2, 125, Morrison, J H Ed , Academic Press, New York.

8) Marshall, J A , Welmaker, G S , Gung, B.W J Am. Chem. Soc. **1991**, 113, 647, and references therein

9) A preliminary account of this work has been published Annunziata, R , Cinquini, M., Cozzi, F , Giaroni, P Tetrahedron Asymmetry **1990**, 1, 355

10) Enders, D., Fey, P , Kipphardt, H Org Synth **1987**, 65, 173

11) Alternative procedures, e.g one step synthesis of **4** from phthalide, or direct conversion of **3** to **5**, gave unsatisfactory yields

12) Slow addition[1] of the chelating aldehyde was not necessary in this case, self-coupling of (S)-**5** occurring to a very limited extent.

13) This procedure did not alter the stereochemical result indeed in some cases the mixtures of diols were isolated and their diastereoisomeric ratios determined by 300 MHz ^{1}H-NMR spectroscopy at 60° (to avoid problems related to slow rotation around the amide bond), the ratios well agreed with those determined for the corresponding lactones

14) However this was not attempted in the case of low-boiling (S)-**2**.

15) The major isomers could generally be obtained diastereoisomerically pure by flash chromatography In the case of compounds **18a, 19a,** and **21a** crystallization upgraded the e.e 's to $\geqslant$96%.

16) Yields and diastereoselections of these reactions were virtually identical to those reported in Scheme 1 and Table 1

17) Asami, M , Mukaiyama, T Chem Lett. **1980**, 17

18) Deoxygenation of a ca. 1 1 mixture of **18a,b** also gave (S)-**26** thus showing that **18b** (and thus **19b-23b**) has the absolute stereochemistry indicated in Scheme 1

19) In agreement with this hypothesis, preliminary experiments indicated that an increase of the steric requirements of the chiral auxiliary leads to an increased enantioselectivity

20) An unfavourable interaction between two aromatic rings could account for the high stereoselection found in the case of the benzyl derivative **7**.

21) Kunz, H., Waldmann, H., Klinkhammer, U Helv Chim. Acta **1989**, 72, 121

22) During the completion of this work, Professor Pedersen reported the cross coupling of chiral α-[(alkoxy carbonyl)amino]aldehydes with aliphatic aldehydes as an entry to aminopolyols Konradi, A W., Pedersen, S.F. J. Org. Chem **1990**, 55, 4506.

23) Wuts, P.G.M., Bigelow, S S J Org. Chem. **1983**, 48, 3489.

24) Kobayashi, Y., Takasa, M , Ito, Y , Terashima, S Bull.Chem Soc.Jpn. **1989**, 62, 3038.

25) Grauert, M , Schollkopf, U. Annalen **1985**, 1817

26) Garner, P , Park, J.M. Synth Comm **1987**, 17, 189.

27) In the absence of **1**, (S)-**3** self couples in low yield and with poor stereocontrol. However, a β-methoxy group greatly enhance the tendency of an aromatic aldehyde toward self coupling [1,2] The possibility that intramolecular chelation is responsible for this behaviour has been suggested [1,2]

28) Reetz, M T Angew Chem. Int Ed Engl. **1984**, 23, 556.

29) Keck, G E , Castellino, S Tetrahedron Lett **1987**, 281.

30) Masamune, S , Choy, W., Pedersen, J.S., Sita, L.S. Angew. Chem. Int. Ed. Engl. **1985**, 24, 1

31) The poor stereoselectivity of the reaction of (R)-**39** with (R)-**5** indicated that this is indeed the mis-matching pair.

32) Racemic 2-phenylpropanal and 3-methyl-2-phenylthiobutanal react with **5** with fair stereoselection.

33) Soai, K., Oyamada, H.; Ookawa, A. Synth. Comm. **1982**, 12, 463.

34) Nunami, K I., Suzuki, M.; Yoneda, N. J Org. Chem. **1979**, 44, 1887.

35) Suigh, A.; Andrew, L.J.; Keefer, R.M., J. Am. Chem. Soc. **1962**, 84, 1179.

36) Colonge, J., Boisde, P. Bull. Soc. Chim. Fr. **1956**, 1337.