Pergamon

Tetrahedron 54 (1998) 5651–5666

TETRAHEDRON

First Enantioselective Addition of Diethylzinc and Dimethylzinc to Prostereogenic Ketones Catalysed by Camphorsulfonamide-Titanium Alkoxide Derivatives †

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Received 9 February 1998; revised 9 March 1998; accepted 12 March 1998

Abstract: The reaction of diethylzinc or dimethylzinc with prostereogenic ketones, in the presence of a stoichiometric amount of titanium tetraisopropoxide and a catalytic amount (20%) of camphorsulfonamide derivatives as chiral ligands leads to the formation of the corresponding enantioenriched *tert*-alcohols with enantiomeric ratios up to 94.5 : 5.5. The best results were obtained when phenones are used as substrates independently of the dialkylzinc reagent. The enantioselectivity shows a linear relationship with the enantiomeric excess of the ligand and seems to be independent of the reaction yield. A tentative catalytic cycle and mechanistic model are proposed for this new reaction.

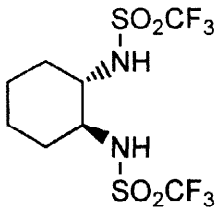
INTRODUCTION

Enantioselective catalytic transformations which involve carbon-carbon bond formation are probably one of the most attractive for organic synthesis. Concerning this subject, the stereoselective addition of dialkylzinc to aldehydes, promoted mainly by chiral aminoalcohols[1] or titanium derivatives[2] [having chiral ligands such as ditriflamides (**1**),[3] TADDol (**2a**),[4] binaphthol (**3**),[5] norephedrine derivatives (**4a**,**b**),[6] and camphorsulfonamide derivatives (**5a**)[7]] have been amply and exhaustively studied. However, although a large number of biologically active natural products contain quaternary carbon atoms,[8] the asymmetric synthesis of tertiary alcohols by the addition of carbon nucleophiles to ketones has achieved considerably less success using chiral ligands[9] and, for example, the enantioselective addition of unreactive dialkylzinc to ketones failed when chiral aminoalcohols[10] were used as promoters, making this subject an unexplored and open challenge.

† This paper is dedicated to the memory of our friend Professor Nino Fava.

0040-4020/98/$19.00
PII: S0040-4020(98)00236-1

On the other hand, the following facts are known: (a) alkyltitanium(IV) alkoxides add smoothly to ketones at room temperature[11] giving the expected tertiary carbinols, (b) mixtures of diethylzinc and titanium tetraalkoxide form ethyltianium(IV) alkoxide derivatives to some extent,[12] and (c) titanium(IV) alkoxides derived from chiral diols act as Lewis acids in the catalytic reduction of ketones.[13] These three considerations prompted us to study the possibility of promoting the enantioselective addition of unreactive dialkylzinc to ketones in the presence of titanium alkoxide and some chiral ligands. In this paper, we will describe the first enantioselective addition of dialkylzinc to prostereogenic ketones.[14]



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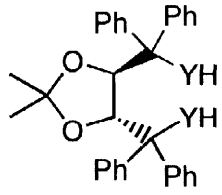
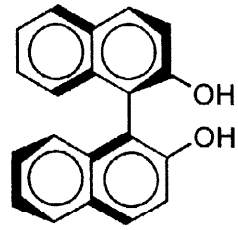


2a: Y = O
2b: Y = $NCOCF_3$



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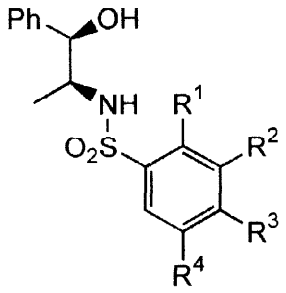
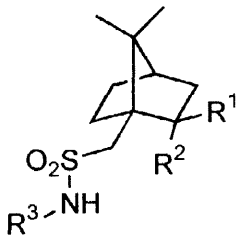


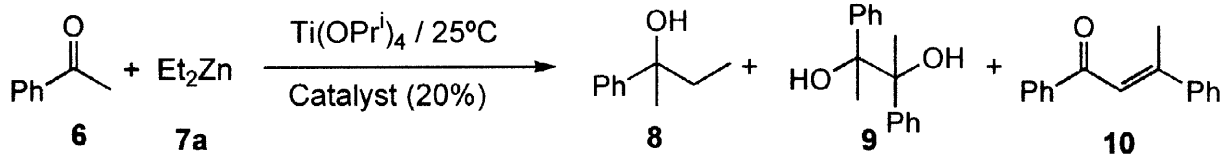
4a: $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$
4b: $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$
4c: $R^1 = OH$, $R^2 = R^4 = Cl$, $R^3 = H$



5a: $R^1 = OH$, $R^2 = H$, $R^3 = Benzyl$
5b: $R^1 = OH$, $R^2 = H$, $R^3 = 1\text{-}Naphthylmethyl$
5c: $R^1 = H$, $R^2 = OH$, $R^3 = 1\text{-}Naphthylmethyl$

RESULTS AND DISCUSSION

We first found that the addition of diethylzinc to acetophenone took place at room temperature (see Scheme 1) in the presence of a catalytic amount of camphorsulfonamide derivative **5a** and an excess of titanium tetraisopropoxide after 2 days with a 56% yield and enantiomeric ratio of 88.5:11.5 (Table 1, entry 1), the main by-product being the corresponding pinacol-type compound **9**. In a subsequent series of experiments acetophenone and diethylzinc were chosen as standard reagents of the process to optimise the reaction conditions.



Scheme 1

Table 1. Enantioselective Addition of Diethylzinc to Acetophenone. Solvent and Catalyst Effect.

Entry	Catalyst	Solvent	time (d)	Yield (%)[a]				e. r. $S:R$[b]
				6	**9**	**10**	**8**	
1	**5a**	$PhCH_3$	2	0	44	0	56	88.5 : 11.5
2	**5a**	CH_2Cl_2	5	10	50	25	6[c]	83.5 : 16.5
3	**5a**	THF	5	0	0	**96**	0	-
4[d]	**5a**	$PhCH_3$	1	8	38	0	42	49.0 : 51.0
5	**1**	$PhCH_3$	0.6	0	40	0	15	50.0 : 50.0
6	**2a**	$PhCH_3$	3	0	94	0	2[c]	40.5 : 59.5
7	**2b**	$PhCH_3$	3	0	78	0	20	48.0 : 52.0
8	**3**	$PhCH_3$	3	0	95	0	3[c]	67.5 : 32.5
9	**4a**	$PhCH_3$	3	35	60	0	0	-
10	**4b**	$PhCH_3$	3	0	88	5[c]	0	-
11	**4c**	$PhCH_3$	3	35	60	0	5[c]	59.0 : 41

[a] Isolated yield after bulb to bulb distillation. [b] Absolute configuration determined by comparison of the optical rotation of alcohol **8** with literature data,[9e] the e.r. was determined by GLC using β-CD column. [c] Deduced from GLC analysis. [d] Instead of using diethylzinc, triethylaluminium was used as source of nucleophile.

When the solvent was changed by methylene chloride or THF, the conversion of acetophenone was slower (Table 1, entries 2 and 3) and only in methylene chloride was it possible to detect the expected addition product with a quite similar enantiomeric ratio (e.r.). In the case of using THF as solvent, the only product detected was the α,β-unsaturated ketone **10**. When the source of nucleophile was changed, using triethylaluminium[15] instead of diethylzinc, the conversion was faster but the expected carbinol was isolated as a racemic mixture (Table 1, entry 4); probably in this case the species generated after interchange between triethylaluminium and titanium tetraisopropoxide is a better Lewis acid than the corresponding camphorsulfonamide-titanium alkoxide derivative. After finding toluene as the best solvent, other ligands were prepared. Thus, the reaction using (*S,S*)-ditriflamide **1** gave a low yield of the expected racemic alcohol **8** (Table 1, entry 5). When the reaction was performed with (*R,R*)-TADDol (**2a**) as chiral ligand, the yield was poor, being the e.r. of the expected alcohol **8** 40.5 : 59.5. In the case of using the (*R,R*)-carboxamide derivative **2b**[16] the yield was better than in the former case but the expected carbinol was almost racemic

(Table 1, entries 6 and 7). Using (*M*)-binaphthol (**3**) as chiral ligand, the expected alcohol **8** was detected in a poor yield and the e.r. was only 67.5 : 32.5 (Table 1, entry 8). When the reaction was carried out using the hydroxysulfonamide derivatives **4a** and **4b**, the alcohol **8** was not detected. However, with the tridentate derivative[17] **4c** the yield and the e.r. were 5% and 59.0 : 41.0 respectively.

Once the hydroxycamphorsulfonamide derivative **5a** was found to be the best ligand and toluene as the appropriate solvent for the enantioselective addition of diethylzinc to ketones, other parameters such as temperature, structure of camphorsulfonamide and of titanium alkoxide, stoichiometry and salt effect were studied (see Table 2). Thus, when the reaction was carried out at high temperature (60°C), the e.r. decreased a little bit, giving a similar chemical yield (compare entry 1 in Table 1, and entry 1 in Table 2). At low temperatures (4 or -15°C) the e.r. increased up to 92.0 : 8.0 (Table 2, entries 2 and 3). However, whereas the enantioselectivity was similar at 4 or -15°C, the chemical yield at the last temperature was significantly lower. When the reaction was carried out at room temperature, but using a stoichiometric amount of the ligand **5a**, the e.r. was a little bit better, the chemical yield being increased up to 89% in only one day (compare entry 1 in Table 1 and entry 4 in Table 2). This result would indicate that the slowest step in the addition involves the presence of the hydroxysulfonamide ligand at the titanium center. The deprotonation of the hydroxysulfonamide ligand with calcium hydride[6] did not change either yield or selectivity (compare entry 1 in Table 1 and entries 2 and 3 in Table 2 with entries 5, 6, and 7 in Table 2, respectively). The use of a more crowded ligand such as **5b** gave a better yield and, in this case, the presence of calcium hydride as base additive improved the e.r., making the rate of reaction slower (compare entries 2, 8 and 9 in Table 2). This result would indicate that the formed alkoxidetitanate derivative competes with the ethyltitanium species in the addition step. Ligand **5c**, having the hydroxy group in the *endo* position, gave very poor chemical yield and e.r. (Table 2, entry 10), the same behaviour being observed when benzaldehyde was used as electrophilic reagent.[7] When the reaction was carried out using only 0.2 equivalents of titanium tetraisopropoxide the yield dropped down to 18%, the e.r. being the same as when one equivalent of titanium was added (Table 2, entry 11): this fact indicates that it is necessary to have an excess of titanium tetraisopropoxide to renew the active species,[7,18] acting as a scavenger for the *tert*-alkoxide anion. After verifying the importance of the amount of titanium tetraisopropoxide, other achiral titanium alkoxides were tested. Thus, when the reaction was performed with a less crowded titanium compound as titanium tetrapropoxide,[19] the main product was the diol **9**, although the *tert*-alcohol **8** could be isolated in a low yield and e.r. In the case of using a more crowded titanium alkoxide, such as titanium tetra *tert*-butoxide,[20] the rate of enantioselective addition was slower and after 10 days the alcohol **8** was isolated in 59% yield and an e.r. worse than the case of using titanium tetraisopropoxide, the main byproduct being the ketone **10** (compare entries 9, 12 and 13 in Table 2). Finally, the same reaction was carried out using the *ent*-**5b** giving similar yield and e.r. This fact proves the

utility of this kind of chiral ligand to get the desired enantiomer by choosing the appropriate ligand enantiomer.

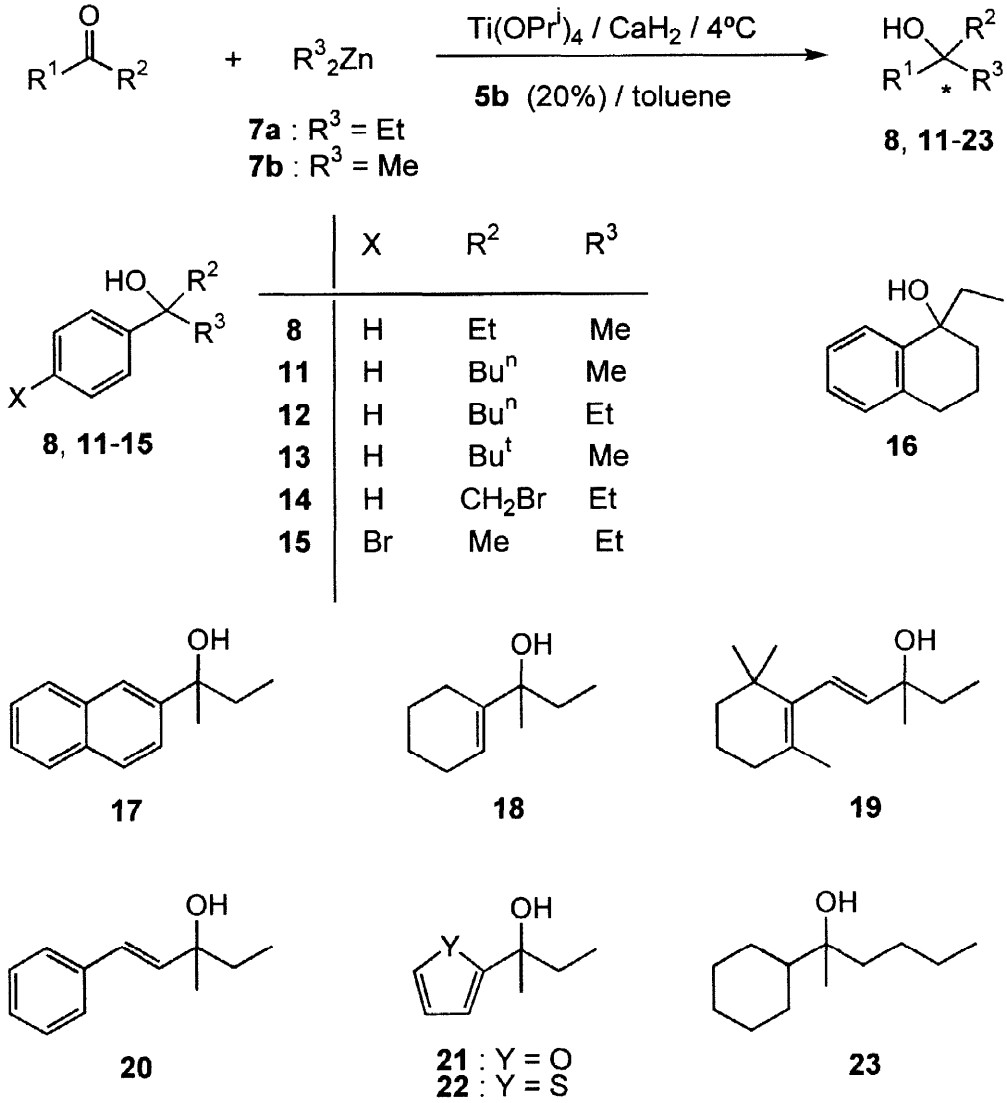
Table 2. Enatioselective Addition of Diethylzinc to Acethophenone. Temperature and Salt Effect.

					Yield (%)[a]			
Entry	Catalyst	Salt	T(°C)	t (d)	**6**	**9**	**8**	e. r. *S* : *R*[b]
1	**5a**	-	60	0.1	0	40	58	86.0 : 14.0
2	**5a**	-	4	5	0	38	60	92.0 : 8.0
3	**5a**	-	-15	12	45	37	11	91.0 : 9.0
4	**5a**[c]	-	25	2	0	10	89	90.0 : 10.0
5	**5a**	CaH_2	25	2	0	46	52	90.0 : 10.0
6	**5a**	CaH_2	4	4	10	19	63	92.0 : 8.0
7	**5a**	CaH_2	-15	12	43	43	9	90.0 : 10.0
8	**5b**	-	4	4	0	12	85	91.0 : 9.0
9	**5b**	CaH_2	4	4	12	16	71	93.0 : 7.0
10	**5c**	-	4	4	0	90	4[d]	67.0 : 33.0
11[e]	**5b**	CaH_2	4	4	66	4[d]	18	93.0 : 7.0
12[f]	**5b**	CaH_2	4	4	13	53	30	82.5 : 17.5
13[g,h]	**5b**	CaH_2	4	10	20	0	59	88.0 : 12.0
14	*ent*-**5b**	CaH_2	4	4	6[d]	13	77	8.0 : 92.0

[a] Isolated yield after bulb to bulb distillation. [b] Absolute configuration determined by comparison of the optical rotation of alcohol **8** with literature data,[9e] the e.r. was determined by GLC using β-CD column. [c] One equivalent of ligand **5a** was used. [d] Deduced from GLC analysis. [e] Only 0.2 equivalents of $Ti(OPr^i)_4$ were used. [f] $Ti(OPr^n)_4$ were used. [g] $Ti(OBu^t)_4$ was used. [h] Ketone **10** was isolated in 14% yield.

Once the conditions for the enantioselective addition of diethylzinc to acetophenone were optimised (Table 2, entry 9), other ketones were submitted to the enantioselective addition of dimethyl and diethylzinc. From the results presented in Table 3 several characteristics must be pointed out, such as: (a) The reaction took longer when dimethylzinc was used instead of diethylzinc, but the enantiomeric ratio was similar in both cases (Table 2, entry 9 and Table 3, entries 1-3). The reaction with a bulky ketone such as *tert*-butyl phenyl ketone occurred only at high temperatures (60°C), yielding a racemic mixture of the corresponding alcohol **13** (Table 3, entry 4). The presence of a bromine atom in the ketone did not change the yield but the e.r. decreased slightly: this fact might be attributed to the presence of a second basic function on the electrophile[7] and not necessarily to any class of electronic effects[21] (Table 3, entries 5 and 6). When the reaction was carried out using α-tetralone (Table 3, entry 7) the yield was poor and was not improved with longer reaction times, however the enantiomeric ratio was the best in this series: this behaviour would be attributed to the

basicity of the alkyltitanium derivative formed *in situ*.[11a] The reaction with a large aromatic moiety in the ketone, as 2-acetylnapthalene, gave a good chemical yield but the e.r. was worse than for other phenyl ketones (Table 3, entry 8), indicating that the catalyst is quite sensitive to steric hindrance . When the electrophilic phenones were changed for the corresponding α,β-unsaturated one (Table 3, entries 9-11), the enantiomeric ratio decreased. The reaction with ketones having a five-membered ring heteroaromatic moiety (Table 3, entries 12 and 13) gave a low e.r. and it might be attributed, as above, to the basicity of the heteroatom in the ring: the more basic the heteroatom the less e.r. was found.[7] Finally, the reaction with a less reactive dialkyl ketone only took place at 60°C after 3 days, yielding the expected alcohol in a low yield and as a racemic mixture.



	X	R^2	R^3
8	H	Et	Me
11	H	Bu^n	Me
12	H	Bu^n	Et
13	H	Bu^t	Me
14	H	CH_2Br	Et
15	Br	Me	Et

Scheme 2

Table 3. Enantioselective Addition of Dialkylzinc to Ketones Catalysed by Hydroxycamphorsulfonamide **5b**.

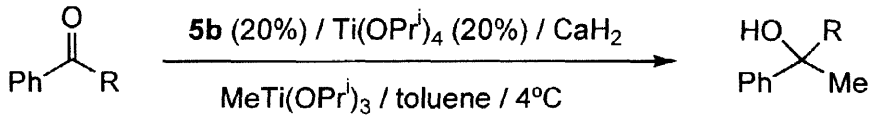
				tert-Alcohol		
Entry	R^3	Ketone	t (d)	no.	Yield (%)[a]	e.r.[b]
1	Me	PhCOEt	14	**8**	89	5.5 : 94.5
2	Me	$PhCOBu^n$	17	**11**	95	91.5 : 8.5
3	Et	$PhCOBu^n$	6	**12**	78	93.0 : 7.0
4	Me	$PhCOBu^t$	2[c]	**13**	3[d]	50.0 : 50.0
5	Et	$PhCOCH_2Br$	4	**14**	79	12.0 : 88.0[e]
6	Et	$4\text{-}BrC_6H_4COCH_3$	7	**15**	83	9.5 : 90.5
7	Et	α-Tetralone	14	**16**	25	5.5 : 94.5
8	Et	2-Acetylnaphthalene	4	**17**	75	29.0 : 71.0[e]
9	Et	1-Cyclohexenyl methyl ketone	6	**18**	36	75.5 : 24.5
10	Et	β-Ionone	7	**19**	75	56.0 : 44.0
11	Et	(*E*)-4-Phenyl-3-buten-2-one	7	**20**	72	65.5 : 34.5
12	Et	2-Acetylfuran	7	**21**	81	43.5 : 56.5
13	Et	2-Acetylthiophene	4	**22**	42	71.5 : 28.5
14	Me	Butyl cyclohexyl ketone	3[c]	**23**	26[f]	50.0 : 50.0

[a] Isolated yield after bulb to bulb distillation. [b] The e.r. were determined by GLC using β-CD column and are given following the elution order. [c] The reaction was performed at 60°C. [d] Deduced from GLC analysis. [e] Determined by GLC using γ-CD column. [f] Starting ketone was recovered in 69% yield.

The role of zinc in the reaction was tested by the experiments outlined in Scheme 3. The reaction of an excess of recently distilled methyltitanium triisopropoxide[11a] (3 equivalents) with propiophenone or valerophenone afforded the expected products after 17 days, with a similar yield to those prepared by reaction with dimethylzinc but as a racemic mixture. This fact might be interpreted considering that the rates of addition of nucleophile by the catalysed or uncatalysed pathway are similar and the concentration of alkyltitanium derivative must be low to avoid the uncatalysed process. The role of zinc reagent seems to make the concentration of the titanium nucleophile species constant and low by a series of different equilibriums, and not to be involved in the product-forming step.[18,22]

It must be pointed out that the preferential addition in methyl or ethyl aryl ketones occurs from the *Si*-face independently of the dialkylzinc reagent (Table 2 and entries 1, 5 and 6 in Table 3), the aryl moiety having preference to the alkyl group. However, in the case of valerophenone the addition occurs from the *Re*-face (Table 3, entries 2 and 3), the reaction again being independent of the dialkylzinc reagent used. The absolute configuration was determined by comparison of optical rotation alcohols **8**,[9e] **11**[23] and **12**[9e] with the

literature data, as well as by reduction of bromoalcohols **14** and **15** to the alcohol **8** by a naphthalene-catalysed lithiation reaction.[24]



8: R = Et, Yield 76%
11: R = Bu^n, Yield 88%

Scheme 3

Once a satisfying degree of optimisation for the reaction had been accomplished, we became curious about the mechanistic aspects of this enantioselective addition. One of the puzzling questions was whether the reactive species is affected by the product,[5b,13c] and another was whether the above reactive species is a mono- or a polynuclear complex.[25] Therefore, the correlation of the yield with the enantiomeric excess of the product **8** (Figure 1) and the correlation of the enantiopurity of the ligand **5b** with the enantiomeric excess[26] of the product **8** (Figure 2) were checked, under the conditions shown in Scheme 2. It seems to be that the product did not change the properties of the catalytic species, the e.r. being constant and independent of yield. In addition, the enantiomeric excess of the ligand shows a direct influence on the enantiomeric ratio of the product. A linear relationship is usually taken as evidence for the involvement of only one chiral ligand in the product-forming step. Other linear correlations[27] have been observed for several titanium promoted reactions with different ligands.[28]

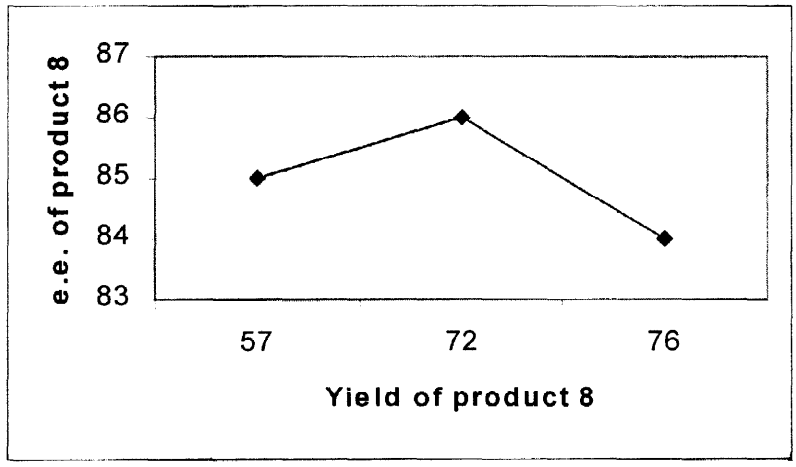


Figure 1

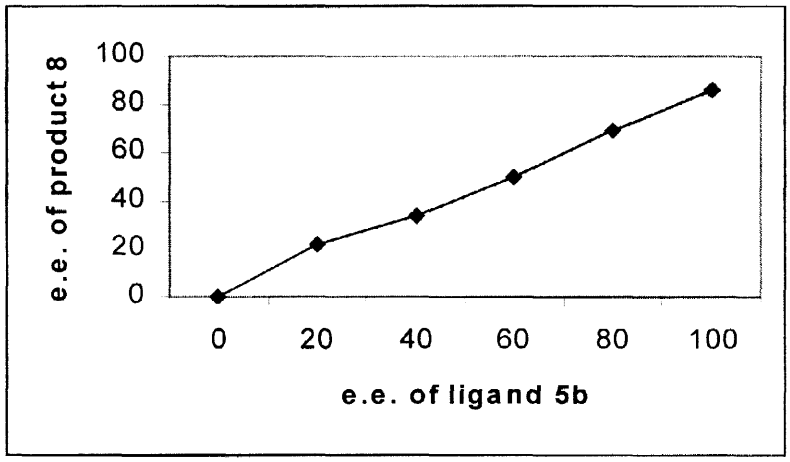
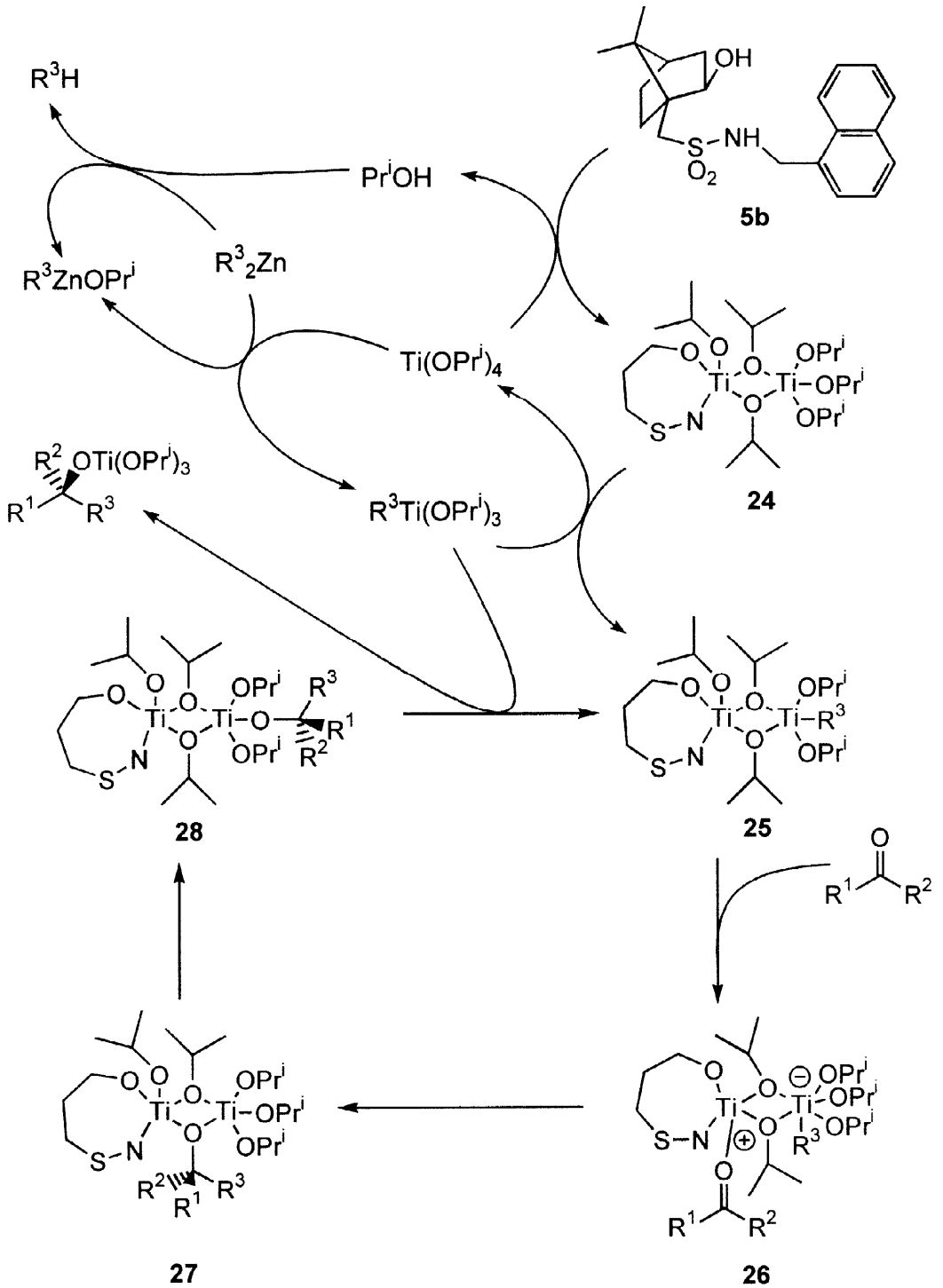


Figure 2

NMR experiments showed the presence of several species in solution. Thus, the reaction of the ligand **5b** with one equivalent of titanium tetraisopropoxide in toluene at 60°C followed by azeotropic removal of isopropanol and toluene showed, in deuterobenzene, the signals of two main different ligand derivatives and another two in a smaller amount. The addition of an extra equivalent of titanium tetraisopropoxide only slightly changed the former ^{1}H-NMR. However, the further addition of a large excess of titanium alkoxide derivative (5 equivalents) provokes the appearance of a main ligand-product, which was originally one of the minor ones. Finally, the addition of acetophenone did not change the last ^{1}H-NMR.

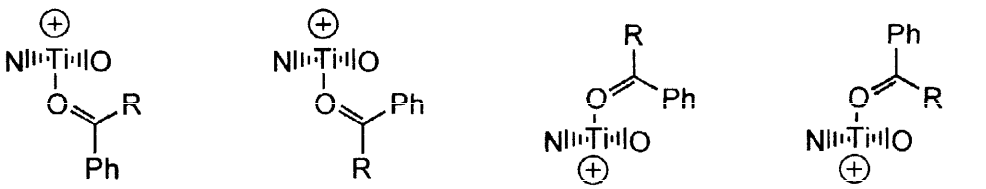
Based on the findings reported here and considering pentacoordinate cationic titanium complexes as part of the catalytic active species,[22c] a plausible catalytic cycle for this new reaction is depicted in Scheme 4. The reaction of titanium isopropoxide with the chiral ligand yields a dititanium species (**24**), which by ligand interchange with some alkyltitanium species affords the precatalyst (**25**) being the alkyltitanium species obtained by ligand interchange between dialkylzinc and titanium tetraisopropoxide.[12] The addition of ketone to the coordination sphere of the more acid titanium center in **25** resuts in formation of the catalytic species **26**. Kinetically, the *trans* position respect to the isopropoxide is rather labile for a substitution, and the lability of this *trans* ligand ensures the effectiveness of titanium alkoxide derivatives for subsequent reactions.[29] The addition of the alkyl moiety (R^3) to the activated carbonyl compound in the above complex, giving **27**, is the enantio-determining step in the catalytic cycle. Then, several successive interchanges of ligand on the titanium centers to give **28**, including a zinc-titanium ligand interchange, renews the precatalyst **25**.



Scheme 4

To complete this study, the complexation of acetophenone on the cationic titanium complex were discriminated by molecular mechanics calculation,[30] and only four relative minimum energetic arrangements appeared. The less energetic structure presented the possibility of a *Si*-attack and in this arrangement the phenyl moiety was located close and in a *quasi*-parallel position respect to naphthyl group. In the case of

valerophenone, the less energetic structure was different, the *Re*-attack being preferred. The different selectivities obtained with different ketones are compatible with this model, the ideal substrate for this system being an aryl alkyl ketone. The arrangement **A** might be stabilised by a π-stacking effect and a hydrogen bond between the oxygen of ligand and the methyl or methylenic hydrogens of the ketone.[31] Highly branched alkyl groups such as *tert*-butyl are subject to steric interactions and a higher temperature is needed to perform the reaction giving a racemic mixture. Long chain unbranched alkyl substituents proceed with a topicity opposite to that found in all the other cases, *Re* instead of *Si* carbonucleophile transfer. In this case the less energetic arrangement is **B**.



A-arrangement	**B**-arrangement	**C**-arrangement	**D**-arrangement
Si-attack	*Re*-attack	*Si*-attack	*Re*-attack
Relative Energy:	Relative Energy.	Relative Energy:	Relative Energy:
R = Me 100.0	R = Me 103.2	R = Me 115.5	R = Me 118.8
R = Bu^n 116.1	R = Bu^n 100.0	R = Bu^n 119.1	R = Bu^n 123.2

Scheme 5

In conclusion, the first method for the enantioselective addition of dialkylzinc reagents to ketones with, in some cases, high enantioselectivity is presented here. The advantages of this methodology are: (a) readily accessible ligand (both enantiomers), (b) temperatures close to room temperature and (c) for use of the catalyst without loss of activity (the ligand is recovered in 90-99% yield after flash column or crystallisation). A catalytic cycle and a simple stereochemical model for the enantioselective additions of dialkylzinc derivatives to ketones to afford the corresponding *tert*-alcohols is proposed.

EXPERIMENTAL SECTION

General.- For general information see ref 7. The chiral ligands **1**,[12] **2b**,[16] **4a,b**,[6,32] **5a**[5] and methyltitanium triisopropoxide[11a] were prepared according to the literature procedures. Butyl cyclohexyl ketone was prepared from cyclohexanecarbonyl chloride by successive reaction with pyrrolidine and butyllithium under standard conditions.[33] ^1H and ^{13}C NMR spectra were recorded using $CDCl_3$ as solvent (unless otherwise stated). The enantiomeric ratios (e.r.) were determined by GLC using nitrogen as carrier gas and P=120 kPa, with a 50 m WCOT fused silica capillary column (0.25 mm diam, 0.25 μm film thickness, CP-cyclodextrin-β-2,3,6-M-19) β-CD, $T_{injector}$=250°C, $T_{detector}$=260°C: A conditions T_{column}=110°C (5 min) and 110-220°C (0.8°C/min); B conditions T_{column}=100°C (20 min) and 100-220°C (0.3°C/min); C conditions

T_{column}=110°C (20 min) and 110-220°C (0.3°C/min); D conditions T_{column}=100°C (30 min) and 100-220°C (0.1°C/min); E conditions T_{column}=90°C (5 min) and 90-220°C (0.8°C/min); F conditions T_{column}=70°C (20 min) and 70-220°C (0.5°C/min); or with a WCOT fused silica capillary column (0.25 mm diam, 0.25 μm film thickness, FS-Lipodex-E) γ-CD, $T_{injector}$=250°C, $T_{detector}$=260°C: G conditions T_{column}=140°C (5 min) and 140-210°C (0.5°C/min); H conditions T_{column}=140°C (5 min) and 140-210°C (0.2°C/min).

Preparation of (1'S,2'S)-N-(2'-Hydroxy-1'-methyl-2'-phenylethyl)-3,5-dichloro-2-hydroxybenzenesulfonamide (**4c**)[31].- To a solution of norephedrine (5 mmol, 0.75 g) in dry ether (5 ml) at 0°C was added triethylamine (5.2 mmol, 0.73 ml), and then a solution of 3,5-dichloro-2-hydroxybenzenesulfonyl chloride (5.1 mmol, 1.33 g) in ether (10 ml). The temperature was allowed to rise to 20°C overnight, and then the mixture was hydrolysed with water (50 ml) and the resulting mixture was extracted with ethyl acetate (3x50 ml). The organic layer was dried over Na_2SO_4 and the solvents were removed under vacuum (15 Torr). The residue was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the titled product (**4c**)[34]: Yield 26%. R_f 0.86 (ethyl acetate), t_r 18.52 min, $[\alpha]^{20}_D$ -8.8 (c=0.7, CH_2Cl_2); ν (film) 3469, 3298 (NH, OH), 3081, 3026, 1696 (HC–C), 1328, 1153 cm^{-1} (SO_2N); δ_H (CD_3COCD_3) 1.02 (3H, d, J = 6.7, CH_3), 3.70-3.75 (1H, m, CHN), 4.75-4.80 (1H, m, CHO), 6.80-7.35 (8H, m, 2xOH, NH, Ph), 7.60, 7.68 (1 and 1H, respectively, 2d, J = 1.8, C_6H_2); δ_C (CD_3COCD_3) 16.3, 57.4, 76.95, 125.3, 125.4, 127.65 (2C), 128.35, 128.85, 129.45 (2C), 130.4, 135.15, 143.25, 202.0; *m/z* 272 (M^+-104, <1%), 107 (12), 77 (12), 44 (100).

Preparation of Camphorsulfonamide ligands **5b**, ent-**5b** *and* **5c**. *General Procedure*[7].- To a solution of 1-naphthylmethylamine (10 mmol, 1.5 ml), isoquinoline (20 mmol, 2.35 ml), triethylamine (11 mmol, 1.6 ml) and DMAP (2 mmol, 0.24 g) in dry DMF (10 ml) at 0°C was slowly added (*ca.* 2 h) another solution of corresponding homochiral 10-camphorsulfonyl chloride (10 mmol, 2.5 g) in dry DMF (10 ml). After 12 h allowing the temperature to rise to 20°C, the mixture was poured into 1 M citric acid solution (50 ml), and the obtained mixture was extracted with ethyl acetate (3x50 ml). The organic layer was washed successively with 1 M citric acid solution (50 ml) and water (2x50 ml), and dried over Na_2SO_4. The solvents were removed under reduced pressure (15 Torr). The residue was dissolved in ethanol (50 ml) at 0°C, and to this mixture was added, with vigorous stirring, sodium borohydride (35 mmol, 1.32 g). The resulting mixture was stirred for 4 h, allowing the temperature to rise to 20°C. The ethanol was removed (15 Torr), and the resulting residue was dissolved in water (50 ml) and extracted with ethyl acetate (3x50 ml). the organic layer was dried over Na_2SO_4 and the solvent was removed (15 Torr) yielding a residue which was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the expected alcohols **5b** and **5c** or *ent*-**5b**. Yields, physical, analytical and spectroscopic data follow.

(1S,2R,4S)-N-(Naphth-1-ylmethyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide (**5b**): Yield 67%. R_f 0.41 (hexane/ethyl acetate 7/3), t_r 25.59 min, mp 114-116°C (ethyl acetate/hexane); $[\alpha]^{20}_D$ -31.4 (c=3.1, CH_2Cl_2); ν (melted) 3534, 3286 (NH, OH), 3048, 3017 (HC=C), 1316, 1139 (SO_2N), 1059 cm^{-1} (CO); δ_H 0.59, 0.86 (3 and 3H, respectively, 2s, 2xCH_3), 0.95-1.05, 1.20-1.70 [1 and 6H respectively, 2m, $(CH_2)_2CHCH_2$], 2.62, 3.22 (1 and 1H, respectively, 2d, J = 13.7, CH_2S), 3.19 (1H, s, OH), 3.95-4.05 (1H, m, CHO), 4.65-4.80 (2H, m, CH_2N), 5.15 (1H, t, J = 5.8, NH), 7.20-7.60, 7.75-7.90, 8.00-8.10 (4, 2 and 1H, respectively, 3m, ArH); δ_C 19.6, 20.25, 27.2, 30.25, 38.85, 44.2, 45.2, 48.5, 50.2, 52.7, 76.3, 123.15, 125.25, 126.05, 126.75, 127.05, 128.8, 129.05, 131.0, 131.95, 133.85; *m/z* 355 (M^+-18, 1%), 157 (21), 156 (100), 155 (22), 154 (27), 141 (25), 129 (14), 107 (11), 93 (12), 79 (10), 55 (11), 44 (22), 43 (16) . (Found: C, 67.64; H, 7.50; N, 3.47; S, 8.41. $C_{21}H_{27}NO_3S$ requires: C, 67.53; H, 7.29; N, 3.75; S, 8.58).

(1S,2S,4S)-N-(Naphth-1-ylmethyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide (**5c**): Yield 5%. R_f 0.33 (hexane/ethyl acetate 7/3), t_r 26.21 min, mp 154-156°C (ethyl acetate/hexane); $[\alpha]^{20}_D$ +16.0 (c=0.5, CH_2Cl_2); ν (melted) 3498, 3289 (NH, OH), 3056 (HC=C), 1317, 1145 (SO_2N), 1040 cm^{-1} (CO); δ_H 0.60, 0.62 (3 and 3H, respectively, 2s, 2xCH_3), 0.90-0.95, 1.20-1.35, 1.45-1.55, 1.60-1.70, 2.05-2.15, 2.20-2.30 [1, 2, 1, 1, 1 and 1H, respectively, 6m, $(CH_2)_2CHCH_2$], 2.81 (2H, s, CH_2S), 3.30 (1H, s, OH), 3.90-4.00 (1H, m, CHO), 4.70-4.75 (2H, m, CH_2N), 5.65 (1H, s, NH), 7.35-7.60, 7.75-7.90, 8.05-8.10 (4, 2 and 1H,

respectively, 3m, ArH); δ_C 18.45, 20.0, 23.45, 28.0, 38.25, 43.7, 45.25, 50.7, 51.15, 56.4, 74.85, 123.25, 125.25, 126.05, 126.7, 127.2, 128.75, 129.0, 131.05, 132.05, 133.8; *m/z* 221 (M^+-152, 2%), 156 (36), 154 (12), 57 (14),44 (100), 43 (30), 42 (12) (Found: C, 67.42; H, 7.11; N, 3.42; S, 8.45. $C_{21}H_{27}NO_3S$ requires: C, 67.53; H, 7.29; N, 3.75; S, 8.58)

(1R,2S,4R)-N-(Naphth-1-ylmethyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide (ent-**5b**): Yield 69%. $[\alpha]^{20}_D$ +30.9 (*c*=3.1, CH_2Cl_2).

Preparation of tert-*Alcohols* **8**, **11-23** *by Enantioselective Addition of Dialkylzinc to Ketones. General Procedure.*- In a 100 ml Schlenk tube equipped with a magnetic stirring bar, camphorsulfonamide **5b** (1mmol, 0.38 g) was dissolved in dry toluene (15 ml) under an argon atmosphere and CaH_2 (2.4 mmol, 0.1 g) was added to the above solution at room temperature. The stirring was continued during *ca* 2 h until no more gas evolved, and then, $Ti(OPr^i)_4$ (6.5 mmol, 1.9 ml, 1 mmol, 0.29 ml in the case of using methyltitanium triisopropoxide) was added. The resulting mixture was cooled down to 0°C and dialkylzinc (12 mmol) or methyltitanium triisopropoxide (15 mmol, 3.6 g) was added. After 5 min at this temperature the corresponding ketone (5 mmol) was added. Then, The Schlenk tube was placed into the refrigerator (4°C). After several days (see Table 1, 2 and 3 and text) the reaction mixture was successively quenched with methanol (2 ml), and a saturated NH_4Cl solution (20 ml). The resulting mixture was filtered through celite, extracted with ethyl acetate (3x50 ml) and the organic layer dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure (15 Torr) and the residue was distilled bulb to bulb and/or purified by flash column chromatography (silica gel, hexane/ethyl acetate) to afford the expected *tert*-alcohol. Yields are included in Tables 1, 2, 3 and Scheme 3, physical and spectroscopic data, as well as literature references, follow.

2-Phenyl-2-propanol (**8**):[9e] R_f 0.61 (hexane/ethyl acetate 7/3), t_r 7.40 min, bp 110-115°C (0.1 Torr); t_r (*S*-**8**) 31.9 min, t_r (*R*-**8**) 32.5 min (conditions A); $[\alpha]^{20}_D$ -9.2 [*c*=3.2, $CHCl_3$, e.r. (*S*/*R*) 93.0 : 7.0]; ν (film) 3413 (OH), 3083, 3060, 3027 (HC=C), 1030 cm^{-1} (CO); δ_H 0.75 (3H, t, *J* = 7.3, CH_2CH_3), 1.50 (3H, s, CH_3C), 1.79 (2H, q, *J* = 7.3, CH_2), 2.16 (1H, s, OH), 7.15-7.20, 7.25-7.35, 7.35-7.45 (1, 2 and 2H, respectively, 3m, Ph); δ_C 8.0, 29.15, 36.3, 74.55, 124.6 (2C), 126.1, 127.7 (2C), 147.45; *m/z* 150 (M^+, <1%), 132 (11), 121 (30), 117 (20), 77 (12), 57 (11), 51 (12), 44 (15), 43 (100).

2-Phenyl-2-hexanol (**11**):[23] R_f 0.64 (hexane/ethyl acetate 7/3), t_r 9.33 min, bp 135-140°C (0.1 Torr); t_r (*R*-**11**) 100.9 min, t_r (*S*-**11**) 102.2 min (conditions B); $[\alpha]^{20}_D$+7.11 [*c*=3.7, CH_3COCH_3, e.r. (*R*/*S*) 91.5 : 8.5]; ν (film) 3417 (OH), 3093, 3061, 3036 (HC=C), 1028 cm^{-1} (CO); δ_H 0.83 (3H, t, *J* = 7.0, CH_2CH_3), 1.50-1.40 [4H, m, $(CH_2)_2CH_3$], 1.52 (3H, s, CH_3C), 1.70-1.80 (2H, m, CH_2C), 1.96 (1H, s, OH), 7.20-7.45 (5H, m, Ph); δ_C 13.9, 22.95, 26.05, 30.0, 43.85, 74.6, 124.7 (2C), 126.3, 128.0 (2C), 148.05; *m/z* 178 (M^+, 1%), 131 (22), 122 (12), 121 (100), 118 (38).

3-Phenyl-3-heptanol (**12**):[9e] R_f 0.68 (hexane/ethyl acetate 7/3), t_r 10.09 min, bp 150-155°C (0.1 Torr); t_r (*R*-**12**) 53.9 min, t_r (*S*-**12**) 54.4 min (conditions A); $[\alpha]^{20}_D$ -1.79 [*c*=2.4, CH_3OH, e.r. (*R*/*S*) 93.0 : 7.0]; ν (film) 3482 (OH), 3062, 3024 cm^{-1} (CO); δ_H 0.75, 0.82 (3 and 3H, respectively, 2t, *J* = 7.3, $2xCH_3$), 0.95-1.05, 1.10-1.45, 1.65-1.95 (1, 2 and 6H, respectively, 3m, $4xCH_2$, OH), 7.15-7.55 (5H, m, Ph); δ_C 7.7, 13.9, 23.05, 25.55, 35.3, 42.2, 77.05, 125.3 (2C), 126.1 (2C), 127.9, 146.05; *m/z* 175 (M^+-17, <1%), 163 (81), 145 (13), 136 (11), 135 (100), 132 (12), 117 (16), 105 (15), 91 (23), 85 (14), 77 (24), 57 (81), 51 (11), 43 (35).

3,3-Dimethyl-2-phenyl-2-butanol (**13**):[9e] R_f 0.61 (hexane/ethyl acetate 7/3), t_r 9.07 min, bp 135-140°C (0.1 Torr); t_r (1^{st}) 98.05 min, t_r (2^{nd}) 103.8 min (conditions C); ν (film) 3473 (OH), 3095, 3058, 3032 (HC=C), 1068 cm^{-1} (CO); δ_H 0.92 [9H, s, $C(CH_3)_3$], 1.58 (3H, s, $OCCH_3$), 2.12 (1H, s, OH), 7.15-7.35, 7.40-7.45 (3 and 2H, respectively, 2m, Ph); δ_C 25.05, 25.65 (3C), 37.85, 78.4, 126.2, 126.95 (2C), 127.0 (2C), 146.15; *m/z* 163 (M^+-15, 2%), 122 (12), 121 (100), 105 (12), 77 (189, 57 (21), 51 (13), 43 (99).

1-Bromo-2-phenyl-2-butanol (**14**):[9e] R_f 0.71 (hexane/ethyl acetate 7/3), t_r 10.62 min, bp 140-145°C (0.1 Torr); t_r (*R*-**14**) 31.24 min, t_r (*S*-**14**) 31.86 min (conditions G); $[\alpha]^{20}_D$ +9.91 [*c*=2.5, CH_3COCH_3, e.r. (*R*/*S*) 12.0 : 88.0]; ν (film) 3549 (OH), 3039, 3067, 3027 cm^{-1} (HC=C); δ_H 0.77 (3H, t, *J* = 7.3, CH_3), 1.80-2.10 (2H, m, CH_3CH_2), 2.44 (1H, s, OH), 3.74, 3.79 (1 and 1H, respectively, 2d, *J* = 10.4, CH_2Br), 7.20-7.40 (5H, m, Ph);

δ_C 8.0, 33.1, 45.9, 75.65, 125.35 (2C), 127.25, 128.25 (2C), 142.5; *m/z* 202 (M^+-26, 4%), 201 (45), 199 (47), 135 (100), 120 (39), 91 (31), 78 (18), 77 (30), 65 (11), 57 (84), 51 (24), 43 (27).

2-(4-Bromophenyl)-2-butanol (**15**):[9e] R_f 0.63 (hexane/ethyl acetate 7/3), t_r 10.38 min, bp 155-160°C (0.1 Torr); t_r (*R*-**15**) 289.4 min, t_r (*S*-**15**) 290.3 min (conditions D); $[\alpha]^{20}_D$ -10.19 [*c*=2.2, CH_3OH, e.r. (*R*/*S*) 9.5 : 90.5]; ν (film) 3423 (OH), 3074, 3049, 3030 (HC=C), 1009 cm^{-1} (CO); δ_H 0.77 (3H, t, *J* = 7.3, CH_2CH_3), 1.49 (3H, s, CH_3C), 1.78 (2H, q, *J* = 7.3, CH_2), 1.90 (1H, s, OH), 7.28, 7.42 (, 2 and 2H, respectively, 2d, *J* = 8.5, C_6H_4); δ_C 8.1, 29.55, 36.55, 74.6, 120.3, 126.8 (2C), 131.05 (2C), 146.7; *m/z* 230 (M^++2, 1%), 228 (M^+, 1), 199 (36), 131 (11), 57 (11), 51 (11), 43 (100).

1-Ethyl-1,2,3,4-tetrahydro-1-naphthol (**16**):[9e] R_f 0.56 (hexane/ethyl acetate 7/3), t_r 10.52 min, bp 150-155°C (0.1 Torr); t_r (1^{st}) 67.6 min, t_r (2^{nd}) 69.0 min (conditions A); $[\alpha]^{20}_D$ -1.61 [*c*=2.3, CH_3OH, e.r. ($1^{st}/2^{nd}$) 5.5 : 94.5]; ν (film) 3417 (OH), 3070, 3021, 1644 cm^{-1} (CO); δ_H 0.86 (3H, t, *J* = 7.6, CH_3), 1.70-2.10, 2.60-2.80 (7 and 2H, respectively, 2m, 4xCH_2, OH), 7.00-7.25, 7.45-7.50 (3 and 1H, respectively, 2m, C_6H_4); δ_C 8.5, 19.6, 29.85, 34.8, 35.2, 72.55, 126.1, 126.2, 126.85, 128.75, 136.8, 142.1; *m/z* 159 (M^+-17, 4%), 158 (29), 147 (41), 143 (14), 130 (22), 129 (100), 128 (38), 127 (12), 115 (17), 91 (21).

2-(2-Naphthyl)-2-butanol (**17**):[9e] R_f 0.83 (hexane/ethyl acetate 7/3), t_r 13.03 min, bp 160-165°C (0.1 Torr); t_r (1^{st}) 109.44 min, t_r (2^{nd}) 110.59 min (conditions H); $[\alpha]^{20}_D$ -5.49 [*c* = 9.5, CH_3OH, e.r. ($1^{st}/2^{nd}$) 29.0 : 71.0]; ν (film) 3445 (OH), 3056 cm^{-1} (HC=C); δ_H 0.80 (3H, t, *J* = 7.5, CH_2CH_3), 1.61 (3H, s, $OCCH_3$), 1.80-2.05 (3H, m, CH_2, OH), 7.35-7.60, 7.70-7.90 (3 and 4H, respectively, 2m, ArH); δ_C 8.3, 29.7, 36.45, 75.0, 123.25, 123.7, 125.55, 125.9, 127.4, 127.75, 128.1, 132.2, 133.1, 145.1; *m/z* 200 (M^+, 3%), 182 (43), 167 (39), 165 (19), 155 (16), 153 (15), 152 (22), 128 (24), 127 (21), 82 (13), 63 (10), 44 (25), 43 (100).

2-(1-Cyclohexenyl)-2-butanol (**18**):[9e] R_f 0.57 (hexane/ethyl acetate 7/3), t_r 7.48 min, bp 130-135°C (0.1 Torr); t_r (1^{st}) 45.4 min, t_r (2^{nd}) 46.5 min (conditions E); $[\alpha]^{20}_D$ +0.70 [*c*=3.0, CH_3OH, e.r. ($1^{st}/2^{nd}$) 75.5 : 24.5]; ν (film) 3432 (OH), 3053, 1663 cm^{-1} (HC=C); δ_H 0.78 (3H, t, *J* = 7.3, CH_2CH_3), 1.25 (3H, s, CCH_3), 1.50-1.65, 1.90-2.10 (7 and 4H, respectively, 2m, 5xCH_2, OH), 5.65-5.75 (1H, m, CH); δ_C 8.15, 22.3, 23.05, 24.6, 25.05, 26.9, 32.8, 75.25, 119.9, 141.9; *m/z* 154 (M^+, <1%), 125 (30), 107 (11), 67 (13), 44 (10), 43 (100).

(1E)-3-Methyl-1-(2,2,6-trimethyl-1-cyclohexenyl)pent-1-en-3-ol (**19**):[9e] R_f 0.67 (hexane/ ethyl acetate 7/3), t_r 11.08 min, bp 160-165°C (0.1 Torr); t_r (1^{st}) 63.9 min, t_r (2^{nd}) 64.35 min (conditions A); $[\alpha]^{20}_D$ +0.47 [*c*=6.0, CH_3COCH_3, e.r. ($1^{st}/2^{nd}$) 56.0 : 44.0]; ν (film) 3400 (OH), 3030, 1032 cm^{-1} (HC=C); δ_H 0.91 (3H, t, *J* = 7.6, CH_2CH_3), 0.99 [6H, s, $C(CH_3)_2$], 1.31 (3H, s, $OCCH_3$), 1.40-1.50, 1.55-1.75, 1.90-2.05 (2, 8 and 2H, respectively, 3m, 4xCH_2, CH_3C=C, OH), 5.46, 6.03 (1 and 1H, respectively, 2d, *J* = 16.5, CH=CH); δ_C 8.4, 19.25, 21.3, 27.75, 28.6, 28.65, 32.55, 33.9, 35.3, 39.3, 73.5, 124.9, 127.8, 137.05, 140.3; *m/z* 222 (M^+, 2%), 204 (46), 189 (28), 161 (10), 147 (22), 135 (11), 134 (16), 133 (55), 121 (26), 120 (16), 119 (100), 109 (13), 107 (18), 105 (39), 95 (23), 93 (19), 91 (34), 81 (17), 79 (18), 77 (18), 69 (25), 67 (13), 65 (12), 57 (12), 55 (42), 53 (16), 44 (21), 43 (58).

(1E)-3-Methyl-1-phenylpent-1-en-3-ol (**20**):[9e] R_f 0.58 (hexane/ethyl acetate 7/3), t_r 10.16 min, bp 155-160°C (0.1 Torr); t_r (1^{st}) 63.5 min, t_r (2^{nd}) 63.95 min (conditions A); $[\alpha]^{20}_D$ -3.94 [*c*=6.7, CH_3COCH_3, e.r. ($1^{st}/2^{nd}$) 65.5 : 34.5]; ν (film) 3428 (OH), 3089, 3070, 3026 cm^{-1} (HC=C); δ_H 0.91 (3H, t, *J* = 7.6, CH_2CH_3), 1.34 (3H, s, CCH_3), 1.63 (2H, q, *J* = 7.6, CH_2) 1.84 (1H, s, OH), 6.24 (1H, d, *J* = 16.2, *CH*CHPh), 6.56 (1H, d, *J* = 16.2, C*H*Ph), 7.15-7.45 (5H, m, Ph); δ_C 8.25, 27.45, 35.25, 73.25, 126.05, 126.25 (2C), 127.15, 127.2, 128.4 (2C), 136.45; *m/z* 176 (M^+, 2%), 158 (40), 147 (42), 144 (10), 143 (83), 142 (14), 141(15), 130 (11), 129 (100), 128 (91), 127 (24), 115 (25), 91 (21), 77 (21), 65 (10), 63 (10), 51 (23), 43 (42).

2-(2-Furyl)-2-butanol (**21**):[9e] R_f 0.53 (hexane/ethyl acetate 7/3), t_r 4.87 min, bp 80-85°C (0.1 Torr); t_r (1^{st}) 63.58 min, t_r (2^{nd}) 64.61 min (conditions F); $[\alpha]^{20}_D$ -0.66 [*c*=3.5, CH_3COCH_3, e.r. ($1^{st}/2^{nd}$) 43.5 : 56.5]; ν (film) 3401(OH), 3111 (HC=C), 1159, 1007 cm^{-1} (CO); δ_H 0.84 (3H, t, *J* = 7.6, CH_2CH_3), 1.52 (3H, s, CH_3), 1.87 (2H, q, *J* = 7.6, CH_2), 2.03 (1H, s, OH), 6.18 (1H, d, *J* = 3.7, CHC=C), 6.30 (1H, dd, *J* = 18, 3.7, *CH*=CHO), 7.34 (1H, d, *J* = 1.8, CHO); δ_C 8.45, 25.8, 34.35, 71.9, 104.55, 109.9, 141.4, 159.45; *m/z* 140 (M^+, 9%), 122 (19), 111 (100), 95 (11), 79 (11), 77 (12), 43 (94).

2-(2-Thienyl)-2-butanol (**22**):[9e] R_f 0.60 (hexane/ethyl acetate 7/3), t_r 7.60 min, bp 105-110°C (0.1 Torr); t_r (1^{st}) 63.11 min, t_r (2^{nd}) 64.35 min (conditions B); $[\alpha]^{20}_D$ -2.76 [*c*=1.5, CH_3COCH_3, e.r. ($1^{st}/2^{nd}$) 71.5 : 28.5]; ν (film) 3427 (OH), 3102, 3070 cm^{-1} (HC=C); δ_H 0.88 (3H, t, *J* = 7.3, CH_2CH_3), 1.60 (3H, s, $OCCH_3$), 1.88

(2H, q, J = 7.3, CH_2), 2.55 (1H, s, OH), 6.85-6.95, 7.15-7.20 [2 and 1H, respectively, 2m, $CHS(CH)_2$]; δ_C 8.5, 29.6, 37.4, 74.05, 122.3, 123.65, 126.55, 153.2; *m/z* 156 (M^+, 1%), 138 (28), 127 (20), 123 (24), 111 (26), 109 (13), 45 (34), 44 (83), 43 (100).

2-Cyclohexyl-2-hexanol (**23**):[9e] R_f 0.74 (hexane/ethyl acetate 7/3), t_r 10.18 min, bp 130-135°C (0.1 Torr); t_r (1st) 94.91 min, t_r (2nd) 95.81min (conditions B); ν (film) 3434 (OH), 1143 cm^{-1} (CO); δ_H 0.91 (3H, t, J = 6.7, CH_2CH_3), 0.96-1.90 (21 H, m with s at 1.08, 8xCH_2, CHOH, CH_3CO); δ_C 14.1, 23.35, 23.95, 25.45, 26.55, 26.75, 26.8, 26.85, 27.5, 39.6, 47.2, 74.35; *m/z* 169 (M^+-15, <1%), 127 (26), 109 (12), 101 (100), 83 (31), 71 (10), 67 (18), 59 (15), 58 (15), 57 (16), 55 (51), 45 (68), 43 (68).

ACKNOWLEDGMENT

This work was financially supported by the DGICYT (Project PB94-1514) from the Spanish Ministerio de Educación y Cultura (MEC). DJR thanks MEC for a fellowship.

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