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Synthesis, Conformational Studies and Enantioselective Homogeneous Catalytic Hydrogenation with CRC-PHOS, and Some Congeners

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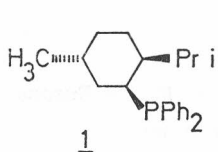
The lactone of (1S,3R)-1-hydroxy-1-diphenylphosphino metyl-2,2,3-trimethylcyclopentan-3-carboxylic acid (*8*, CRC-PHOS), and (1R,3R)-bis(diphenylphosphinoxymethyl)-2,2,3-trimethylcyclopentane (*16*), were prepared starting from (+)-camphanic and (—)--isocamphoric acid, respectively. Their complex salts [Rh(norbornadiene)lactone of (1S,3R)-1-hydroxy-1-diphenylphosphinomethyl--2,2,3-trimethylcyclopentan-3-carboxylic acid] perchlorate (*27*), and [Rh(norbornadiene (1R,3R)-1,2,2-trimethyl-1,3-bis (diphenylphosphinoxymethyl)cyclopentane)] perchlorate (*28*) were isolated and their catalytic and enantioselective ability tested on some model prochiral carboxylic acids. The asymetric bias did not exceed 35% e. e. in either case. Attepmts at preparation of the diphosphine congener of *16*, i. e. *21*, as well as isolation of the phosphinite congener of *8*, i. e. *22*, failed. NMR LIS study of the conformation in solution of *8*, and model compounds *6* and *9* revealed that *6* and *8* possess in their most stable conformations a dihedral angle ψ of 165°, (Figure 4.) while for *9* two stable conformations with ψ 200° and 350° are found. These results indicate that bidentate binding of metal to heteroatom X (O, P) in the side chain, and to the tetrahedral oxygen within lactone group is scarcely possible.

INTRODUCTION

After the discovery of the $Rh(PPh_3)_3$ Cl complex as a highly efficient achiral homogeneus hydrogenation catalyst,[1] numerous successful uses of soluble Rh-complexes with chiral phosphine ligands have been reported.[2,3] Their enantioselectivity vary greatly, depending on the proper spatial compatibility between substrate and chiral catalyst. Present knowledge in this particular field was recently rationalized.[4,5] It appears that proper rigidity of the ligands within the catalytic complex may assure a predominant chiral topology of the system, as a consequence of the transfer of steric restraint from the remote asymmetric atoms to the whole molecular framework[6,7] Low enantioselectivity of the first unidentate phosphines[8,9] (e. g. *1*), as well as

the increase in enantioselectivity on going to unidentate monophosphines which are capable of additional interaction *via* oxygen atoms[10] (e. g. *2*), or to bidentate diphosphines[11,12] (e. g. *3*), or to bidentate diphosphines with two additional possibilities for coordination (e. g. *4*), could be explained by the enhanced rigidity and the chiral topology within the catalytic complex.[13] The role of oxygen atom within the methoxy groups in *2* and *4* is not completely clear, however. Thus *2* gave 81% enantiomeric excess (e. e.) in a particular asymmetric reduction while use of *2* (where 2-methoxyphenyl was replaced by 2-methyl-4-bromophenyl group) still afforded 74% ee.[14] X-Ray structure determination of a complex 4-Rh-cycloetadienyl (COD)[6] revealed that the methoxy group is too far away for it to be apically bound to rhodium, although the authors suggest that some indefined interaction between the methoxy group and Rh^+ can still take place. Halpern et al.[15] have shown that *N*-acylde-hydroamino acids as substrates bind more strongly to diphosphine-rhodium complex of *4* than to its achiral demethoxy congener (DIPHOS). They attribute this to the methoxy groups present in *4*.



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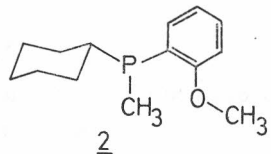

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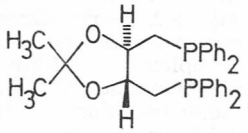

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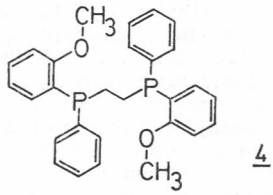


4

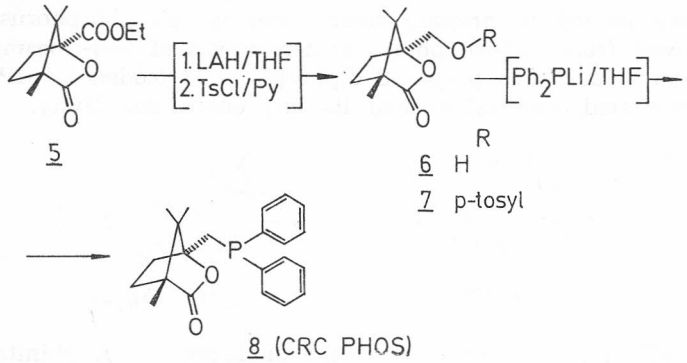
Since the »lock and key« relationship in the field of asymmetric homo-geneous catalytic hydrogenation of various olefins still deserves general acknowledgement, and a beneficial effect from additional interaction in oxygen-containing chiral phosphines may be expected, we recently focused our attention on the synthesis of a new chiral monophosphine *8*, coded CRC-PHOS, since one can expect that such oxygen-containing chiral mono--phosphines may show enhanced effectiveness as a chiral ligand versus non-oxygen containing chiral mono-phospines. A preliminary report on this work has appeared,[16] while this paper reports additional synthetic and struc-tural investigations of CRC—PHOS and some congeners, derived from (+)-camphor.

RESULTS AND DISCUSSION

A. Preparations

According to the reasonable prerequisite of the easy availability of the chiral organic ligand for asymmetric phosphine complexes from natural sources, we first decided to prepare the chiral ligand camphanyl-diphenyl-phosphine i. e. the lactone of (1S,3R)-1-hydroxyl-1-diphenylphosphinomethyl--2,2,3-trimethylcyclopentane carboxylic acid (*8*, CRC—PHOS). It was prepared from the commercially available (+)-camphanic acid,[17] according to the Scheme 1.

SCHEME 1.



5

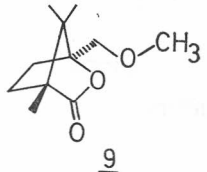
6 R = H

7 R = p-tosyl

8 (CRC PHOS)

(+)-Camphanic acid was introduced by Gerlach[18,19] as an efficient chiral resolving agent, and repeatedly used by others.[20–22] It is, in turn, available from inexpensive nature (+)-camphor.[18,23]

It is remarkable that LAH reduction of the ethyl camphanate[22] (5) proceeded at —10 °C completely regioselectively whereby the lactonic carbonyl group remained essentially uneffected. Introduction of the diphenyl-phosphinic unit in 7 rendered some difficulties, known from similar efforts. When sodium diphenylphosphide (Ph_2PNa), generated from commercially available Ph_2PCl and metallic sodium in THF was used, according to Kagan[11] only hydrolysis of tosylate 7 to the alkohol *6* occured. The same result was obtained when metallic potassium was used, although in some earlier cases it afforded some advantages compared with sodium.[2,24] The best results were obtained when lithiumdiphenylphospide was generated from triphenylphosphine and metallic lithium, while one mole of phenyl-lithium, formed as a side product, was destroyed on addition of tert-butylchloride.[5,25] In this case, however, another side product was formed, and its structure was established as *10*.



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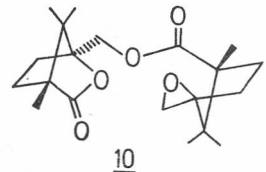
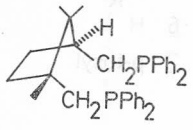


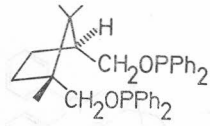
10

In the NMR spectrum it exhibits a characteristic AB quartet for oxiranes[26] at 2.68 and 2.83 ppm as well as five separated singlets for six non- equivalent methyl groups within two camphanic units. Elemental analysis, IR and mass spectra confirmed its structure. Compound *10* was regularly formed at ambient or elevated temperatures, presumably via nucleophilic attack of the alkoxide ion of *6* on the lactone carbonyl group within the second mole of tosylate 7, followed by intramolecular nucleophilic displacement of the tosylate group. Formation of the alkoxide ion had already been noticed in the anomalous attack of a strong base, e. g. hydride ion from LAH, on some sterically crowded tosylates.[27] Careful optimization of the phosphinating conditions (see Experimental) allowed isolation of *8* in 73% yield, as compared

to 53.4% reported previously.[16] However, a series of hydrogenation (see section C) revealed its moderate enantioselectivity for the substrates *23* and *25*. Therefore we turned to prepare some other chiral, phosphorus-containing ligands derived from (+)-camphor i. e. derivatives of (—)-isocamphoric acid (*14*). Morrison et al.[2] have prepared diphosphine *11* (coded CAMPHOS) from (+)-camphoric acid, and established its low enantioselectivity.



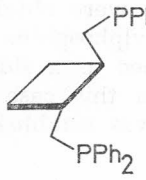
11 (CAMPHOS)



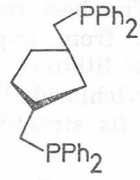
12 (CAMPHINITE)

Johnson et al.[28] recently argued that the analogous diphosphinite *12* (coded CAMPHINITE) might exhibit higher enantioselectivity than the parent dihposphine *11*. The results of enantioselective hydrogenations with *12* did not reveal any enhancement of asymmetric bias in relation to *11*, however.

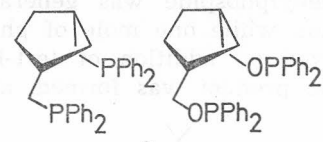
On the other hand, Glaser et al.[7] demonstrated in a series of papers that *trans*-1,2-bis(diphenylphosphinomethyl)cycloalkanes (e. g. *A* and *B*), and some other cyclic bis-phosphines exhibit high enantioselectivity on hydrogenation. Along this line we decided to prepare 1,3-trans isomers *16* and *21* (schematically represented as *D*), and to compare their efficiency as chiral ligands with those 1,3-cis isomers *11* and *12* (schematically represented as *C*). We assumed that the overall topology of the latter is more »symmetric« than of the former, which therefore is expected to exhibit higher enantioselectivity.



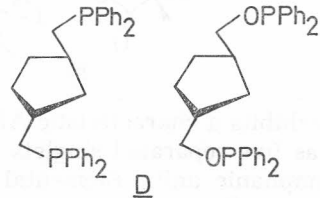
A



B



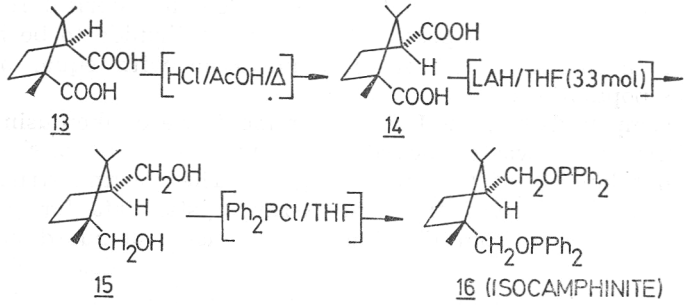
C
(1,3-cis)



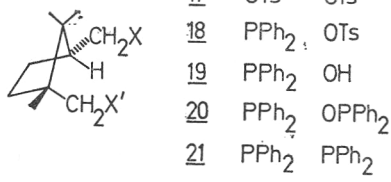
D
(1,3-trans)

To this end we isomerized (+)-camphoric into (—)-isocamphoric acid *14*, following the procedure of Noyes et al.[29] By a similar reaction sequence as described for *6*, diol *15* was prepared (Scheme 2.). To avoid tedious esterification of the neopentyl-type carboxylic group in *14*, free acid has been reduced, and diol *15* was quantitatively transformed into diphosphinite *16*. Bis-diphenylphosphinylation of *15* via tosylate *17* into *21* turned out to be very difficult task,

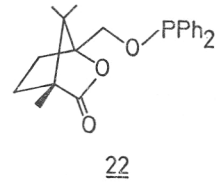
SCHEME 2.



however. The neopentylic group in *17*, in spite of numerous attempts, did not undergo nucleophilic substitution to afford *21*. Instead, mono-phosphines *18* and *19* were regularly isolated as the main products. Having hydroxyphosphine *19* at hand, we tried to prepare a mixed phosphine-phosphinite ligand *20* for hydrogenation experiments; all attempts to isolate this compound failed, however. At last, for comparison with CRC-PHOS *8*, phosphinite derivative *22* was prepared. This compound turned to be extremely unstable, decomposing during isolation of the catalytic complex. Therefore, for structural studies of its metal binding, model compound *9* was prepared. A preliminary series of hydrogenation results with these ligands are reported in section C.



	X	X'
17	OTs	OTs
18	PPh_2	OTs
19	PPh_2	OH
20	PPh_2	$OPPh_2$
21	PPh_2	PPh_2



22

B. Structural Studies

The conformation in solution of *8* (CRC-PHOS) was determined using the LIS-NMR technique. To this end, two model molecules for phosphinite *22*, i. e. *6* and *9*, were submitted to the same measurements, and computer assisted calculations were performed for all three molecules. The bound shifts were obtained by incremental dilution procedure,[30,31] and related to the LSR-substrate complex geometry by the Mc Connell-Robertson equation[32] ($3\cos^2\vartheta - 1)/r^3$; the agreement was expressed in terms of the agreement factor R.[33]

$$R = [\Sigma_i W_i (i_{obsd} - i_{calcd})^2 / \Sigma_i W_i (i_{obsd})^2]^{1/2}$$

The principal magnetic axis was maintained along the lanthanide donor atom bond. Its direction was not changed during calculations since the introduction of additional variable parameters would have rendered the problem poorly determined. For the same reason, we did not carry out any population analysis of side chain conformations. The minima of R we found may represent

an average determined by the population of the conformations present in solution according to the Boltzman distribution.[34]

Furthermore, in our compounds we excluded, for sterical reasons, two--sites metal binding, i. e. the possibility for the lanthanide to be bound from two different positions to the same donor atom with equal or different conformation populations.[35]

For the compounds *8* and *9*, LIS measurements were taken using Eu $(fod)_3$--d_{27}, while Pr$(fod)_3$-d_{27} was employed in measurements with *6*, since Eu$(fod)_3$--d_{27} caused overlapping of the methyl signals. The starting structural parameters were in part derived from the X-ray crystal data for (+)-8-bromocamphor,[36] and in part from Dreiding models using standard bond lengths and bond angles.[37] Five bound shifts, i. e. those of the two diastereotopic protons of the methylene group in the side chain and the three methyl groups, were employed in the calculations for *6* and *8*, while in *9* the methyl of the methoxy group was also considered. Methylene protons on the bicyclic ring, being distant from the possible binding sites, revealed very small bound shifts, and since it was difficult to get accurate values for the bound shifts from the 60 MHz spectra they were not taken into account during computation. The other experimental bound shifts derived by linear regression are given in Table I.

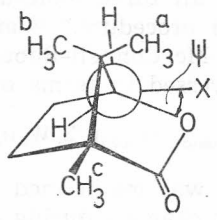
TABLE I

Bound Shifts for Compounds *6*, *8* and *9*[a]

	Compd. *6*	Compd. *8*	Compd. *9*
CH_3	3.21	1.33	5.18
	1.89	0.89	5.20
	2.60	2.07	5.88
CH_2	8.23	2.62	5.85
	9.38	0.53	5.85
O—CH_3			4.38

[a] CH_3 bound shifts are listed according to permutation 1(a,b,c) in Table II. Correlation coefficients were regularly above 0.995.

For all methyl groups a mean position was adopted for the three equivalent protons assuming free rotation of these groups. Conformation of the side chain has been defined by the angle ψ between the C (1) — O bond, within the lactone ring, and C (1′) — X bond (X = O, P) of the side chain (Formula *E*).

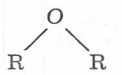
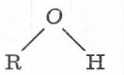
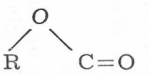
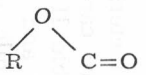
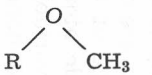


E

In order to attribute properly the singlets of the methyl groups on the bicyclic ring, separate calculations were performed for all possible permutations of the relevent bound shifts as well as for the three possible binding

TABLE II

Agreement Factors for Permutations of CH_3 (a, b, c) Groups and Different Binding Sites in 6, 8 and 9

Permutation No	Order[a]	*6*			*8*		*9*		
									
1.	a, b, c	7.3	16.6	10.4	49.6	36.0	22.6	9.4	55.5
2.	a, c, b	31.1	10.9	*5.3*	*1.4*	40.9	21.1	16.7	51.4
3.	b, a, c	39,4	13.1	11.5	7.7	11.9	13.2	10.1	53.2
4.	b, c, a	44.5	10.8	16.1	24.7	40.3	13.3	10.3	53.0
5.	c, a, b	32.6	*5.9*	*7.6*	37.8	22.6	13.0	*7.5*	14.3
6.	c, b, a	42.5	16.6	15.3	*3.6*	*5.3*	20.0	16.7	16.2

[a] Notation of methyl groups according to formula E.

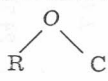
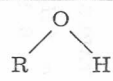
sites, i. e. oxygen atoms in *6* and *9*; in *8* only two binding sites were assumed, since it is known that »soft« phosphorous atom is a poor coordinating site for a »hard« lanthanide ion.[38] At this stage of calculation the bond angle ϑ and the dihedral angle φ of the lanthanide atom, as well as dihedral angle ψ (O—C(1)—C(1′)—X), were considered as variable parameters in the minimization of the R factor, while the lanthanide-donor atom bond distance ϱ was kept constant at 3.0 Å. (Table II).

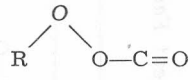
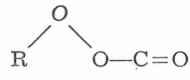
Since it is generally accepted[33] that *R* factors up to 10% represent acceptable agreement, further calculations were carried out only for the cases corresponding to the factors cited in Table II. At this stage ϱ (restricted within the reasonable limits 1.0—4.0 Å), ϑ and φ were employed as variable parameters in the minimization of *R*, while ψ was varied stepwise with increments of 25°. ψ values were then plotted vs. *R* factors and only the minima for $R \leq 10\%$ were considered. For compound *9*, we first optimized the dihedral angle Ω, which defines the position of the methoxy group, by varying it stepwise for each value. Since the optimized value $\Omega = 25°$ was almost independent of ψ, we chose this value in the plot of ψ vs. *R*.

The parameters relative to the minima are listed in Table III.

TABLE III

R Factors and Parameters Defining the Position of the Lanthanide Atom and the Side Chain Conformation in the LSR Complexes with 6, 8 and 9

	Compound *6*								
Binding site	>C=O								
	Perm. No1	Perm. No 5		Perm. No 2		Perm. No 5			
	1[f]	1	2	1	2	1	2	3	
ϱ[a]	2.5	3.1	3.7	1.0	3.7	4.0	1.0	4.0	
ϑ[b]	47.1	83.1	81.0	137.2	136.0	78.4	135.2	145.1	
φ[c]	129.8	214.6	247.3	174.7	207.0	185.2	176.2	214.0	
ψ[d]	215.0	165.0	10.0	140.0	340.0	115.0	190.0	265.0	
R[e]	6.7	5.9	0.8	3.6	3.2	7.4	3.8	3.1	

	Compound *8*						Compound *9*	
Binding site	>C=O							
	Perm. No 2	Perm. No 3	Perm. No 6		Perm. No 6		Perm. No 5	
	1	1	1	2	1	2	1	2
ϱ	2.9	2.7	3.1	2.8	3.8	3.2	2.4	2.7
ϑ	17.4	11.2	17.7	13.6	175.8	119.7	124.3	122.6
φ	308.7	296.6	340.3	323.1	162.2	86.3	198.4	207.8
ψ	115.0	165.0	65.0	140.0	40.0	165.0	350.0	200.0
R	0.3	4.7	3.4	2.1	1.1	1.5	1.9	2.5

[a] Lanthanide-donor atom bond distance in Å.
[b] Lanthanide bond angle in degrees.
[c] Lanthanide dihedral angle in degrees.
[d] Dihedral angle C—X relative to C—O, in degrees, measured clockwise along the C—C bond.
[e] Agreement factor in percentage.
[f] Number of minima for the particular formation.

Since the entries with unlikely parameters, i. e. $\varrho < 2$ Å, $\varrho > 3.2$ Å, $\vartheta < 50$, were rejected, it resulted that the tetrahedral oxygen of the lactone group is the binding site for *6*, *8* and *9*. As can be seen in Table III, good agreement and acceptable ϱ, ϑ, ψ values were obtained in permutation No 6, and minimum No 2 ($\psi = 165^0$) for *8*; permutation No 5 and minima No 1 ($\psi = 350^0$) and No 2 ($\psi = 200^0$) for *9*. The corresponding plots are given in Figures 1—3. Therefrom it turns out that, at variance from 6 and *8*, in *9* the side chain may adopt two average conformations, since both minima correspond to acceptable parameters for the lanthanide atom position.

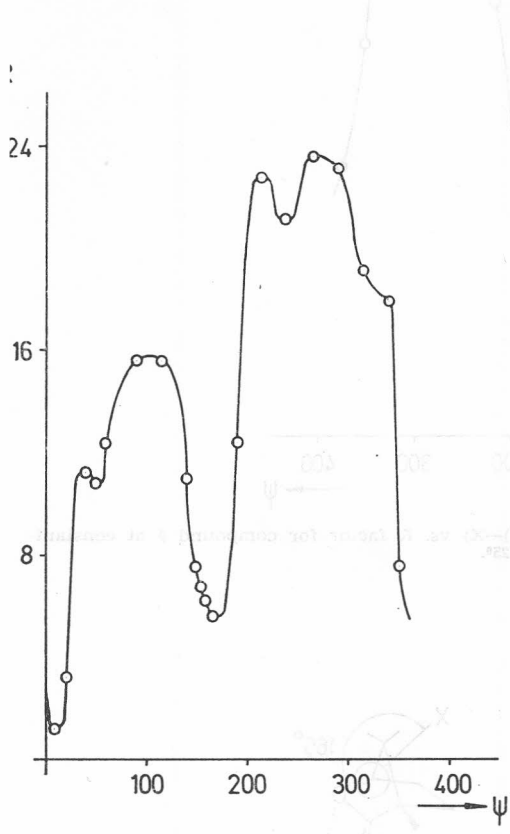


Figure 1. Plot of dihedral angle ψ (O—C(1)—C(1')—X) vs. *R* factor for compound *6*.

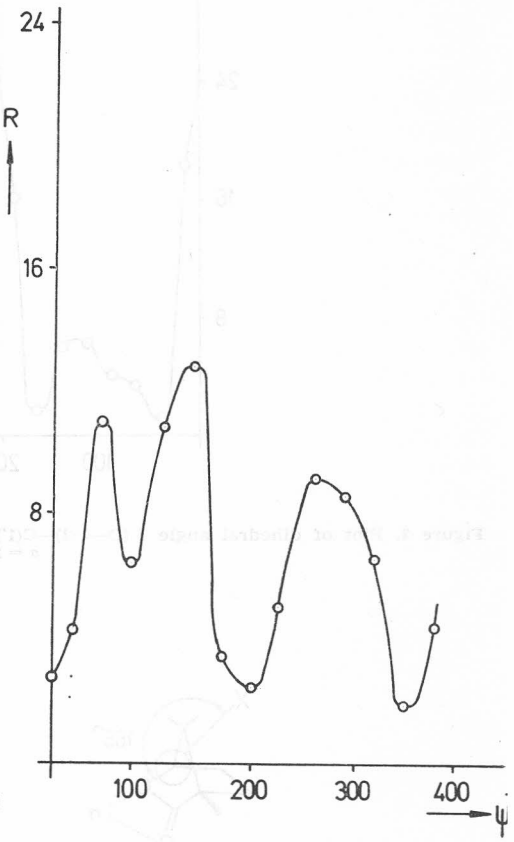


Figure 2. Plot of dihedral angle ψ (O—C(1)—C(1')—X) vs. *R* factor for compound *8*.

A schematic representation of the lanthanide position and side chain conformations in the complexes with *6*, *8* and *9* is given in Figure 4.

The possibility of bidentate complexation of the lanthanide to the lactonic group was examined in terms of the distance between the lanthanide atom and the oxygen atoms for the conformations corresponding to the minimum *R* value (Table IV).

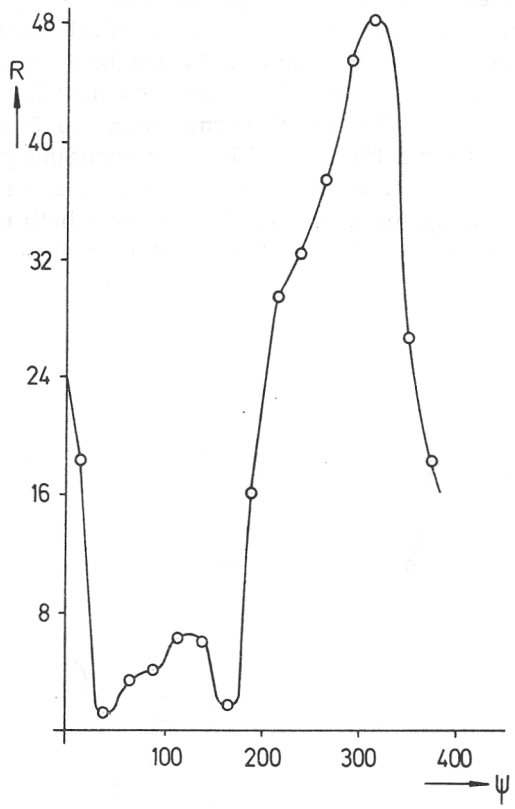


Figure 3. Plot of dihedral angle ψ (O—C(1)—C(1')—X) vs. R factor for compound *9* at constant $\sigma = 25^0$.

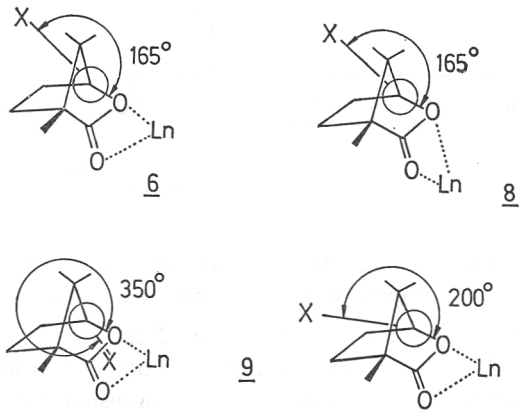


Figure 4. Schematic representation of the conformations of LSR complexes with *6*, *8* and *9*.

TABLE IV

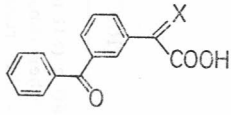
Distance in Å between Lanthanide Atom and Oxigen Atoms in LSR Complexes with 6, 8 and 9

Compound			—OR
6 (55°)	3.2	2.9	6.2
8 (55°)	3.3	5.3	
9 (230°)	2.4	3.6	2.8
9 (20°)	2.7	3.8	5.3

Bidentation involving both lactonic oxygens can be certainly excluded in *8*, in compounds *6* and *9*, though, it cannot be ruled out, since the distances from the carbonyl oxygen are less than 4 Å. Large dihedral angles in all but one conformation of the complexes of *6*, *8* and *9* seem to exclude a bidentate binding at oxygen and phosphorus of CRC-PHOS, or at two oxygen atoms in *9*, respectively.

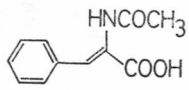
C. *Hydrogenations.*

A cationic complex *27*, [Rh(CRC-PHOS)$_2$NBD] ClO_4 · THF (NBD = norbornadiene) could be crystallized out from the mixture of [(NBD)$_2$ Rh] · ClO_4 and CRC-PHOS in THF on agitation for 1 hr at ambient temperature, and the subsequent addition of *n*-hexane. Complex *27* is a fine orange-red, amorphous powder, which could be manipulated outside of the protecting atmosphere of an inert gas. The set of hydrogenations with the two model substrates *23* and *25* is presented in Table V.

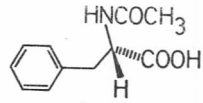


23 CH_2

S-24 H_1CH_3



25



S-26

27

28

The rates of hydrogenation of *23* corresponded approximately to that obtained with (—)-DIOP, (*3*), while *25* was reduced at somewhat lower rates than described.[9] Both products of hydrogenation *24* and *26* possess S-configuration,[9,40] however, low enantiomeric excess was achieved on variation of some reaction parameters.

Complex *27* has been found, however, to exhibit high diastereoselectivity in the hydrogenation of metacycline hydrochloride into 6-α-methyl-6-deoxy-

TABLE V

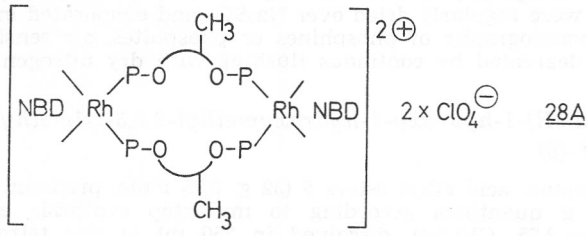
Asymmetric Hydrogenation of 23 *and* 25[a]

Entry	Substrate	Solvent	Catalyst or catalytic system	Substrate/Rh ratio	Press. (atm)	Temp. (°C)	Time (h)	e. e. (%) (config.)
1.	23	EtOH abs./Bz(1 : 2)	*27*	86	95.5	20	23	13.6 (S)
2.	23	EtOH abs.	*27*	86	70.0	20	20	14.9 (S)
3.	23	EtOH abs.	*27*	86	84.0	20	55	3.1 (S)
4.	23	EtOH abs.	*27*	86	14.0	50	13	12.6 (S)
5.	23	EtOH abs.	*27*	86	70.0	2	21[b]	14.1 (S)
6.	23	EtOH abs.	*27*	86[c]	14.0	50	3	13.2 (S)
7.	23	EtOH abs./Bz(4 : 1)	$[RhCl(1,5\text{-}HD)]_2/8$[d]	25	70.0	20	20	9.8 (S)
8.	23	EtOH abs.	*28*	62	70.0	20	15	32.7 (S)
9.	23	EtOH abs./Bz(1 : 1)	$[RhCl(1,5\text{-}HD)]_2/22$[e]	25	70.0	20	18	0
10.	23	EtOH abs./Bz(1 : 1)	$[RhCl(1,5\text{-}HD)]_2/22$[f]	25	70.0	20	18	0
11.	25	EtOH 99.8%	*27*	86	84.0	20	65	3.2 (S)
12.	25	EtOH 99.8%	*27*	86	84.0	20	48	3.4 (S)
13.	25	EtOH 99.8%	*27*	69	70.0	20	16	1.9 (S)
14.	25	EtOH 99.8%	$[RhCl(1,5\text{-}HD)]_2/22$[f]	86	84.0	20	48	6.3 (S)

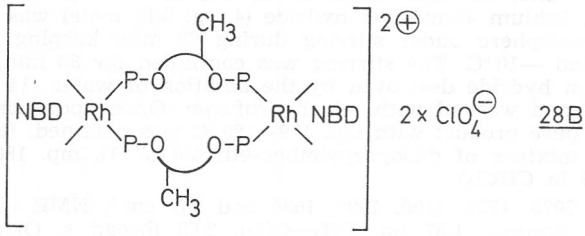
[a] All hydrogenation were carried out with 0.011 g (0.11 mmol) of Et_3N, if not otherwise cited.
[b] Chemical conversion was ca. 80%. In all other runs conversion was quantitative according to TLC.
[c] The total conc. of 23 was 1.12×10^{-2} M, in other runs it was 1.12×10^{-1} M.
[d] The ratio 8/Rh was 2.01.
[e] The ratio 22/Rh was 2.19.
[f] The ratio 22/Rh was 1.10.

-tetracycline. After certain optimization of the reaction conditions, 95% diastereomeric excess of the 6-α-epimer was achieved (see Experimental).

Some further experiments were performed with the analogous complex of *iso*-camphinite *16*, i. e. with *28*. Double enantiomeric bias in hydrogenation of *23*, was achieved, as compared to CRC-PHOS complex *27*, but still low enantioselectivity with *25* (Table III). This complex presumably acts as a diastereomeric mixture of two species (*28 A* and *28 B*), and in none of them is *16* bound as a bidentate ligand to the same Rh atom.



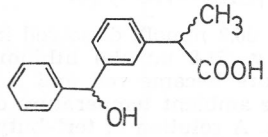
28A



28B

The same possibility should be taken into account for the complex formed in situ with *12*,[28] since bidentate complexations were entropically unfavourable because of the required formation of the ten-membered ring.

The last series of hydrogenation experiments was initiated with a complex of camphan phosphinite *22*. This compound, though presumably formed quantitatively in the reaction mixture (tlc proof) largely decomposed on attempted isolation, a behaviour already noted for some other phosphinite derivatives.[41] Its catalytic complex with $[Rh(NBD)_2]ClO_4$ was unstable and not crystalline; therefore, we performed hydrogenations of *23* with na *in situ* formed complex with $[RhCl(1,5\text{-}HD)]_2$ (HD = hexadiene) in THF as the solvent. Surprisingly, formation of the racemic *24* as the main product was observed. In a separate experiment only $[RhCl(1,5\text{-}HD)]_2$ was employed in the absence of THF as the solvent, affording compound *29* and was accompanied by deposition of the elemental rhodium. This indicated that a presumably low concentration of the complex of $[RhCl(1,5\text{-}HD)]_2$ with phospinite *22* is obtained in the first case, since THF predominantly occupied a free coordination site in the complex. Its elimination as the solvent in preparation of the complex *28* in situ might assure coordination of *??*. Experiments in this direction are underway.



29

EXPERIMENTAL

Melting points were determined on a Kofler microheating stage (Boetius) and have not been corrected. IR spectra (KBr pellets) were obtained with a Perkin Elmer M 297 spectrophotometer, (only strong bands are indicated). NMR spectra were run on a Perkin Elmer R 12 instrument with TMS as an internal standard; shifts are given in ppm values downfield from TMS. Optical rotations were measured on a Perkin Elmer 141 polarimeter at ambient temperature. Thin layer chromatography (TLC) was performed on aluminium plates precoated with Merck silica gel 60 F_{254}. Thick layer chromatography (PLC) was performed on glass plates precoated with silica gel of the same type.

Column chromatography was run over granular silica gel 0.05—0.2 mm (Merck). Organic extracts were regularly dried over Na_2SO_4 and evaporated in vacuo. Solvents used for the chromatography of phosphines or phosphites, air sensitive compounds, were previously deareated by continous flushing with dry nitrogen for 20 min.

Lactone of (1S,3R)-1-hydroxy-1-hydroxymethyl-2,2,3-trimethylcyclopentan-3--carboxylic acid (6)

To the camphanic acid ethyl esters *5* (32 g, 0.15 mole, prepared from camphoric acid in 50—100 g quantities according to multistep synthesis cited in ref. 20, $[\alpha]_D = -18.2^0$ ($c = 2.75$, $CHCl_3$)), dissolved in 250 ml of dry tetrahydrofuran and cooled to —10 °C, lithium aluminium hydride (4.2 g; 0.11 mole) was gradually added in a nitrogen atmosphere under stirring during 60 min, keeping the temperature between —7 °C and —10 °C. The stirring was continued for 30 min, and the excess lithium aluminium hydride destroyed by the addition of water (14 ml). Hydroxides were filtered off and washed with tetrahydrofuran. On evaporation of the filtrate, 24.6 g (88.9%) of pure product with mp. 179—180 °C was obtained. It could be recrystallized from a mixture of diisopropylether-ethanol (3 : 1), mp. 180—181 °C. $[\alpha]_D = +1.06^0$ ($c = 1.9$ in $CHCl_3$).

IR (KBR): 3500, 2975, 1755, 1180, 1095, 1035 and 907 cm^{-1}. NMR ($CDCl_3$): 0.95, 1.10 (2 s, for 3 CH_3 groups), 1.87 (m, CH_2—CH_2), 2.60 (broad s, OH), 3.95 (broad s, CH_2OH).

Anal. $C_{10}H_{16}O_3$ (184.00) calc'd: C 65.19; H 8.75%
found: C 65.31; H 8.84%

Lactone of (1S,3R)-1-hydroxy-1-para-toluensulphonyloxymethyl-2,2,3--trimethylcyclopentan-3-carboxylic acid (7)

To the compound *6* (19.8 g, 0.107 mole), dissolved in 200 ml of anhydrous pyridine and cooled to 0 °C, tosylchloride (30.8 g, 0.162 mole) was gradually added during 60 min under stirring. The mixture was cooled overnight at 0 °C and then poured onto 600 g of ice, diluted with 100 ml of water, and the crude product immediately filtered off. The precipitate was washed with cold water and dried, affording 34.7 g (95.3%) of the white product with mp. 116—117 °C. Recrystallization from 150 ml of 99.8% ethanol gave 33.8 g (92.9%) of the product with the same melting point. IR (KBr): 2980, 1780, 1360, 1193, 1165, 983, 915, 857, 840, 817, 677 cm^{-1}. NMR ($CDCl_3$): 0.88, 0.93, 1.08 (3 s, for 3 CH_3 groups) 1.85 (m, CH_2—CH_2), 2.50 (s, Ar—CH_3), 4.30 (s, CH_2), 7.80 (m, C_6H_4). $[\alpha]_D = +15.8^0$ ($c = 1.9$ in $CHCl_3$).

Anal. $C_{17}H_{22}O_5S$ (338.41) calc'd.: C 60.33; H 6.55%
found: C 60.41; H 6.73%

Lactone of (1S,3R)-1-hydroxy-1-diphenylphosphinomethyl-2,2,3-trimethyl--cyclopentan-3-carboxylic acid (CRC-PHOS) (8)

To triphenylphosphine (6.9 g, 26.3 mmol), dissolved in 30 ml of anhydrous tetrahydrofuran under nitrogen, 0.36 g (51.8 mmole) lithium, divided into small pieces was added, whereupon the mixture became red and has reached 30 °C after 1 hr. It was then allowed to cool to the ambient temperature during the next three hours, followed by cooling in an ice-bath. A solution of tert-butylchloride (0.85 g, 9.18 mmol)

in tetrahydrofuran (5 ml) was added over a 20 min period, keeping the temperature at —10 °C. The mixture was the heated to reflux for 5 min, in order to destroy the phenyllithium. After cooling down to —10 °C, compound 7 (4.5 g, 13.3 mmol), dissolved in 30 ml of tetrahydrofuran, was added over 30 min. The reaction proceeded for 18 hours at —20 °C, the solvent was then evaporated under reduced pressure. To the oily residue, water (30 ml) and benzene (150 ml) previously flushed with nitrogen were added. After 30 min stirring the organic phase was separated, dried, and evaporated under reduced pressure. The residual oil was purified by elution from a 220 g silica column with *n*-hexane-acetone (7 : 3). From it was obtained 3.39 g (72.3%) of pure *8*, as a colourless viscous oil. IR (film): 3050, 2960, 1770, 1430, 1392, 1328, 1105, 1080, 1008, 909, 738, 691 cm^{-1}. NMR ($CDCl_3$): 0.93, 0.98, 1.13 (3 s, for 3 CH_3 groups) 1.23—2.15 (m, CH_2—CH_2), 2.75 (J_{AB} = 2 Hz), 2.35 (J_{BX} = 2 Hz and J_{AB} = 20.0 Hz, —CH_2—P(Ph)$_2$ system ABX : 8 lines, 2dd), $[\alpha]_D^{24}$ = —11.2° (*c* = 1.93 in $CHCl_3$).

Anal. $C_{22}H_{25}O_2P$ (352.42) calc'd: C 74.98; H 7.15%
found: C 74.85; H 7.18%

In some preparations, 5—6% of the compound *10* ($R_f \sim 0.45$) was isolated. It had mp. 157—158 °C, on recrystallization from light petroleum. IR: 2960, 1780, 1720, 1450, 1375, 1285, 1240, 1200, 1170, 1090, 1070, 1020, 905 cm^{-1}. NMR ($CDCl_3$): 0.90, 0.93, 1.12, 1.29 (4 s, CH_3 each), 0.98 (s, 2 CH_3), 1.5—2.6 (m, 4 CH_2), 2.68 and 2.83 (dd, CH_2 oxirane, *J* = 5.0 Hz), 4.41 (broad s, CH_2), M^+ ion 350.

Anal. $C_{20}H_{30}O_5$ (350.44) calc'd: C 68.53; H 8.63%
found: C 68.80; H 9.02%

Lactone of (1S,3R)-1-hydroxy-1-methoxymethyl-2,2,3-trimethyl--cyclopentan carboxylic acid (9)

To compound *6* (2.0 g, 10.8 mmol), dissolved in dry tetrahydrofuran (15 ml), sodium hydride (0.50 g, ca. 11 mmol as 55% suspension in mineral oil) was added, and the resulting suspension was stirred for 30 min at 40 °C. Then dimethylsulphate (0.76 g, 6.0 mmol) was added, and the reaction continued for 30 min at reflux. The cooled reaction mixture was poured into ice-water (100 ml), adjusted to pH 6 with acetic acid, and extracted with ether (3 × 50 ml) .The dried organic extracts were evaporated, and the oily residue distilled at 65—70 °C/2 mmHg affording 1.68 g (78%) of pure *9*, which crystallized on standing. On recrystallization from light petroleum it had mp. 53—54 °C. IR: 2930, 1770, 1445, 1400, 1328, 1170, 1100, 1070, 905 cm^{-1}. NMR ($CDCl_3$): 0.87, 0.98 (2 s, for 3 CH_3 groups), 1.35—2.15 (m, 4H), 3.38 (s, OCH_3), 3.58 (s, CH_2O). $[\alpha]_D$ = + 9.6° (*c* = 1.05 in $CHCl_3$).

Anal. $C_{11}H_{18}O_3$ (198.27) calc'd: C 66.66; H 9.15%
found: C 66.40; H 9.20%

(1R,3R)-1,2,2-Trimethyl-1,3-bis-hydroxymethylcyclopentane (15*)

(1R,3R)-1,2,2-Trimethyl cyclopentan-1,3-dicarboxylic acid *14* (10.0 g, 0.049 mole, prepared according to ref. 29, $[\alpha]_D$ = —44.8° (*c* = 9.72 in EtOH), lit[29] $[\alpha]_D$ = —46.8° (*c* = 9.78 in EtOH)) was dissolved in THF (150 ml). This solution was added under stirring to a suspension of LAH (6.5 g, 0.171 mole) in ether (125 ml), cooled to 5—8 °C, and maintained under a stream of nitrogen. After 20 min. the reaction mixture was heated under reflux for 4 hrs, cooled, water (6 ml) was added dropwise, then 15% NaOH (6 ml). The precipitate was filtered off with a cellite filter-aid, washed with THF, and the filtrate evaporated, 8.5 g of *15* was obtained, which on recrystallization from 20 ml of diisopropylether had m. p. 87—88 °C (7.71 g, 89.6%). IR: 3220 (broad), 2930, 2870, 1445, 1385, 1360, 1020, 990, 975 cm^{-1}. NMR ($CDCl_3$): 0.75, 0.88, 0.93 (3s, 3 CH_3 groups); 3.48 (s, CH_2OH); 3.63 (overlapped dd, CH CH_2OH). $[\alpha]_D$ = — 43.7° (*c* = = 2.2 in $CHCl_3$).

* The numbering of carbon atoms in the cyclopentane ring in this and later compounds in the series, starts with the atom bearing one methyl and one carboxylic group, and is opposite to that in the camphanic acid series (*5—10*) where C(1) atom bears one hydroxyl group!

Anal. $C_{10}H_{20}O_2$ (172.26) calc'd.: C 69.77; H 11.63%
found: C 69.80; H 11.84%

*(1R,3R)-1,2,2-Trimethyl-1,3-bis(*para*-toluensulphonyloxymethyl) cyclopentane* (17)

Compound *15* (1.72 g 10.0 mmol) was dissolved in dry pyridine (16 ml), and para-tosylchloride (6.64 g, 34.8 mmol) was added portionwise at 0 °C during 50 min. After a further 18 hrs of reaction, the mixture was deposited on ice, then poured into water (50 ml), acidified with HCl (1 : 4), and extracted with methylenechloride (3 × 50 ml). The organic extracts were dried, evaporated and the oily residue purified on a 200 g silica gel (*n*-hexane-acetone (7 : 3) as eluent) affording 4.75 g (98%) of pure *17* as an oil which crystallized on standing, m. p. 49—50 °C. $[\alpha]_D = -13.7^0$ ($c = 1.96$ in $CHCl_3$). IR: 2975, 1600, 1360, 1190, 1176, 1098, 952, 835, 815, 667 cm^{-1}. NMR ($CDCl_3$): 0.67, 0.83 (2s, 3 CH_3 groups), 0.90—2.30 (m, 2 × CH_2), 2.48 (s, 2 × ArCH_3), 3.81 (CH_3CCH_2OTs), 4.02 ($CHCH_2OTs$), 7.42, 7.86 (dd, $J_{AB} = 6.0$ Hz).

Anal. $C_{24}H_{32}O_6S_2$ (480.63) calc'd.: C 59.77; H 6.71%
found: C 59.41; H 6.74%

*(1R,3R)-1,2,2-Trimethyl-3-diphenylphosphinomethyl-1-(*para*-toluensulphonyl-oxymethyl)cyclopentane* (18)

Starting from triphenylphosphine and lithium, lithium diphenylphosphide was prepared as described for *8*. The bis-tosylate *17* was then added at —10 °C over 45 min and the reaction was monitored by TLC (cyclohexane-acetone (8 : 2) as eluent; 10% sulfuric acid in methanol as spot indicator). Formation of one product only ($R_f \sim 0.6$) was confirmed. It was isolated after work-up as described for *8*, and purified on a silica gel column with the above solvent system as eluent, affording an oil which crystallized on standing, m. p. 70—71 °C. IR: 3088, 3060, 2930, 2858, 1452, 1437, 1368, 1190, 960, 738, 696, 664 cm^{-1}. NMR ($CDCl_3$): 0.69, 0.73, 0.86 (3s, CH_3 each), 0.90—2.90 (m, 6H, 3 CH_2 groups), 2.46 (s, ArCH_3), 3.73 (CH_3CCH_2OTs), 7.40 (m, 10H), 7.81 (dd, $J_{AB} = 6.3$ Hz, 2H, other 2H superimposed at 7.40) $[\alpha]_D = -72.1^0$ ($c = 1.9$ in $CHCl_3$)

Anal. $C_{29}H_{35}O_3SP$ (496.61) calc'd.: C 70.42; H 7.13%
found: C 70.19; H 7.23%

(1R,3R)-1,2,2-Trimethyl-3-diphenylphosphinomethyl-1-hydroxymethyl cyclopentane (19)

Sodium (0.10 g, 4.3 mmol), and potassium (0.40 g, 10.0 mmol) were fused under nitrogen at 150 °C (oil bath), then after cooling to ambient temperature, dioxane (20 ml) was added drop by drop, followed by triphenylphosphine (1.31 g, 5.0 mmol). The initial deep-red solution turned into a deep-yellow suspension after 3 hrs. stirring. The bis-tosylate *17* (1.0 g, 2.08 mmol) was then added gradually over 20 min. After 45 min stirring at ambient temperature, and 1.5 hrs at reflux, formation of the product with $R_f \sim 0.55$ was completed (cyclohexane-acetone (8 : 2) as eluent). The cooled reaction mixture was filtered through a cellite filter, washed with toluene (2 × 20 ml), the filtrate evaporated, and the residual oil was purified on a silica gel column using the above solvent mixture. It was obtained 0.42 g (59%) of pure *19*, as an oil which slowly crystallized while standing on ice. IR (neat): 3400 (broad), 3075, 3060, 2960, 2875, 1480, 1433, 1367, 1027, 936, 694 cm^{-1}. NMR ($CDCl_3$): 0.61, 0.75, 0.89 (3s, CH_3 each), 0.95—2.70 (m, 4H), 1.45 (s, CH_2P), 1.81 (broad s, OH), 3.31 (s, CH_2OH), 7.4 (broad s, 10H).

Anal. $C_{22}H_{29}OP$ (340.40) calc'd.: C 77.62; H 8.59%
found: C 77.48; H 8.81%

(1R,3R)-1,2,2-Trimethyl-1,3-bis(diphenylphosphinoxymethyl)cyclopentane (16)

To the solution of diol *15* (0.65 g, 3.77 mmol) in THF (9.0 ml) and anhydrous pyridine (0.60 ml, 7.50 mmol), chlorodiphenylphosphine (1.37 ml, 1.64 g, 7.45 mmol) was added drop by drop over 30 min at ambient temperature, under a nitrogen

atmosphere. Soon, pyridinium hydrochloride precipitated which was then filtered off after 1 hr stirring under a nitrogen atmosphere. The filtrate was evaporated to dryness, and the residual oil dried at 0.2 mmHg/P_2O_5. On TLC, only one spot (R_f = = 0.75, *n*-hexane-acetone (7 : 3) as eluent) was visible, indicating a quantitative yield. A sample was purified on a silicagel column using the above solvent mixture for elution. $[\alpha]_D = -32.6^0$ ($c = 0.945$ in CH_2Cl_2). IR (neat): 3060, 3040, 2880, 2840, 1483, 1437, 1395, 1370, 1095, 1025, 1000, 810, 790, 750, 740, 700 cm^{-1}. NMR ($CDCl_3$): 0.88, 0.95 (2s, for 3 CH_3 groups), 1.18—2.08 (m, for 2 CH_2 groups), 3.42—3.98 (m, 2 CH_2O), m 7.2—7.75 (m, 2OH).

Lactone of (1S,3R)-1-hydroxy-1-diphenylphosphinoxymethyl-2,2,3--trimethylcyclopentan-3-carboxylic acid (22)

Alcohol *6* (1.0 g, 5.43 mmol) and pyridine (0.43 g, 5.44 mmol) were dissolved in anhydrous THF (3.0 ml), and the resulting solution was cooled under nitrogen to — 15 °C .Under stirring chlorodiphenylphosphine (1.2 g, 5.44 mmol) was added over 25 min, and stirring was continued for 1 hr. The precipitate was filtered off under nitrogen, the filtrate was evaporated to dryness and the residual oil dried at 0.2 mmHg/P_2O_5, giving a quantitative yield. The product decomposed upon TLC analysis in various solvent system. IR (neat): 2885, 2840, 1780, 1445, 1175, 1135, 1075, 1040, 1020, 910, 700 cm^{-1}. NMR ($CDCl_3$): 0.87, 1.02 (2s, for 3 CH_3 groups), 1.5—2.15 (m, 4H), 3.55—3.78 (m, CH_2O), 7.10—8.15 (m, 10H).

[Rh(norbornadiene)(lactone of (1S,3R)-1-hydroxy-1-diphenylphosphinomethyl--2,2,3-trimethyl)cyclopentan-3-carboxylylic acid$_2$] perchlorate tetrahydrofuran solvate (27)

Rhodiumtrichloride hydrate, $RhCl_3 \cdot H_2O$ (0.25 g, 0.95 mmol) was dissolved in 96% ethanol-water (5 : 1, 40 ml); then 0.7 ml of norbornadiene was added, and the mixture set aside at ambient temperature for 48 hrs. The yellow-brown crystals (0.176 g, 80%) were filtered off and a part (0.137 g, 0.30 mmol) dissolved in methylene chloride (6.0 ml). Then norbornadiene (0.055 g, 0.60 mmol) was added, followed by 0.134 g (0.60 mmol) of silver perchlorate monohydrate. This operation was performed under nitrogen, and the resulting suspension was stirred at ambient temperature for 1 hr. Silver chloride was filtered off, the filtrate evaporated to dryness, and the residue crystallized upon addition of tetrahydrofuran (6.0 ml). The yellow-orange precipitate was collected by filtration and dried to afford 0.13 g (56.7%) of pure $[Rh(NBD)_2]ClO_4$, m. p. 240 °C (dec.), NMR ($CDCl_3$): 1.55 (s, broad, CH_2), 4.20 (s, broad, 2CH), 5.40 (s, broad, 4 = CH).

Compound *8* (0.421 g, 1.19 mmol), was dissolved in dry, de-aerated tetrahydrofurane (10 ml), then 0.233 g (0.60 mmol) of $[Rh(NBD)_2]ClO_4$ was added. After 1 hr stirring at ambient temperature, 20 ml of deaerated *n*-hexane was added via a syringe, and the reaction mixture was stirred for an additional 1 hr at 0 °C. The crystalline product was collected by filtration, washed with *n*-hexane and dried to afford 0.606 g (96%) of the product, m. p. 180—182 °C (crystalls changed during heating). NMR ($CDCl_3$): 0.88, 0.91, 1.09 (3s, CH_3 each), 1.2—2.3 (m, 4H), 2.60 (broad s, P-CH_2), 3.85 (broad s, CH), 4.45 and 4.65 (2 broad s, = CH).

Anal. $C_{51}H_{58}O_8ClP_2Rh \cdot C_4H_8O$ (1071.44) calc'd.: C 61.66; H 6.21%
found: C 61.25; H 6.22%

[Rh(norbornadiene)(1R,3R)-1,2,2-trimethyl-1,3-bis(diphenyl-phosphinoxymethyl)cyclopentane] perclorate (28)

Bis-phosphinite *16* (0.20 g, 0.37 mmol) was dissolved under nitrogen in methylenechloride (6.0 ml), then $[Rh(NBD)_2]ClO_4$ (0.144 g, 0.37 mmol) was added, and the resulting solution stirred 1 hr at ambient temperature. After partial evaporation of the solvent, *n*-hexane (25 ml) was gradually added, and slow crystallization of *29* initiated. After prolonged chilling on ice orange-red crystals were collected by filtration, washed with *n*-hexane and dried, affording 0.302 g (97%) of 28, m. p. 148—149 °C. IR: 2880, 1480, 1438, 1312, 1100, 990, 750, 700, 620 cm^{-1}.

Anal. $C_{41}H_{46}O_6ClP_2Rh$ (835.09) calc'd.: C 58.97; H 5.55%
found: C 58.32; H 6.03%

General hydrogenation procedure

Hydrogenations were performed in a 200 ml Parr general purpose bomb. Depending upon the mode of the preparation of the catalytic complex, i. e. whether it was isolated as a crystalline solid or prepared in situ, two variants of hydrogenation procedure were used.

a) Hydrogenation Using Isolated Catalytic Complex

Prochiral compounds *23* or *25* (1.2 mmol) were dissolved in 10.0 ml of de-aerated solvent (previously purged for 20 min with dry nitrogen), and then 0.014 mmol of the catalytic complex *27* or *28*, and triethylamine (0.108 mmol) were added. The pressure bomb was purged 8 times with hydrogen at the intended working pressure. The outer temperature of the thermostated oil-bath was recorded. The reaction was followed by TLC; for *23* the solvent system chloroform-light petroleum-methanol (5.0 : 3.5 : 1.5) was used, and detection with a UV lamp, while for *25* acetone-methanol (1.0 : 1.0) was used. After quantitative chemical conversion was confirmed, the solvent (or solvent mixture) was evaporated, and the residual mass was purified by PLC using the solvent mixture cited above. After collection of the silica zone containing the crude product, it was extracted with methanol, evaporated, and the residue dissolved in chloroform followed by filtration. The filtrate was evaporated and the residual product dried at 0.2 mmHg/P_2O_5 before determination of the $[\alpha]_D$ value. Enantiomeric excess for *S-24* was calculated on the basis of the reported value ($[\alpha]_D = +57.4$) in ref. 43, measured at $c = 0.75$, in CH_2Cl_2)), while for *S-26* it was based on the value $[\alpha]_D = +46.0$ reported in ref. 4, measured at $c = 1.0$, in EtOH). The isolated yields were regularly over 90%.

b) Hydrogenation with in Situ Prepared Catalytic Complex

To a solution of $[RhCl(1,5\text{-}HD)]_2$ (0.10 g, 0.023 mmol) in 1 ml of de-aerated solvent, were added either 0.032 g (0.091 mmol) of the phosphine *8* in 1 ml of the solvent or 0.036 g (0.099 mmol) of the phosphinite *22*. The mixture was allowed to react for 15 min at ambient temperature under a stream of nitrogen and then injected into a solution of 0.30 g (1.12 mmol) of prochiral compound *23* in 10 ml of solvent containing 0.011 g (0.11 mmol) of Et_3N. The reaction mixture was purged 8 times with hydrogen at the intended working pressure. The reactions were performed at ambient temperature and monitored by TLC (see previous procedure). After quantitative chemical conversion was confirmed, the solvent (or solvent mixture) was evaporated and the product isolated as described above.

Hydrogenation of Metacyclin-hydrochloride into 6-α-Methyl-6-deoxy-5--hydroxytetracycline.

Metacyclin-hydrochloride (5.0 g, 10.44 mmol), dissolved in methanol (30 ml), and de-aerated with a stream of nitrogen was hydrogenated in the presence of 0.10 g (0.093 mmol) of $[Rh(CRC\text{-}PHOS)_2NBD\ ClO_4] \cdot THF$ in an autoclave (200 ml vol.). The contents of the autoclave were purged 8 times with hydrogen at 300 psig, hydrogenation then started at the same pressure. It was conducted at 100 °C for 4 hrs and the completion of the reaction was proven by TLC, using cellulose precoated plates, sprayed with 0.1 M solution of EDTA-sodium. The spots are made visible by a UV_{360nm} lamp, after brief exposure to ammonia vapors. This system revealed the quantitative hydrogenation of the starting metacycline under conditions described above. The product was isolated as the salt of sulfosalycilic acid after the addition of 5.0 g of sulfosalycilic acid, (dissolved in methanol-10 ml) to the reaction mixture (previously evaporated to 15 ml volume). On standing for 12 hrs at 0 °C, the pure product was separated by filtration, the solid washed with methanol, and dried affording 6.3 g of the crystalline sulfosalycilate, $E^{1\%}_{1\,cm} = 247$ at 349 nm. Quantitative chromatography monitoring indicated > 97% purity.

Hydrogenation of 23 with [RhCl(1,5-HD)]$_2$-preparation of 29

Compound *23* (0.22 g, 0.87 mmol) and triethylamine (0.11 g, 1.1 mmol) were dissolved under nitrogen in 7 ml of the solvent mixture benzene/ethanol (1 : 1), and 10 mg (0.022 mmol) of [RhCl(1,5-HD)]$_2$ were added. After flushing with hydrogen (8 times at 70 atm) hydrogenation was performed for 18 hrs at the same pressure. After the usual work-up pure *29* was isolated by PLC using chloroform-light petroleum-methanol (6.0 : 3.5 : 1.5) as eluent, m. p. 103—104 °C. IR (KBr): 3400, 1705, 1235, 1015, 900, 709, 698 cm^{-1}. NMR (DMSO-d_6): 1.34 (d, CH_3); 3.4—3.9 (*m*, HOC*H*); 5.72 (C*H*CH$_3$); 7.10—7.60 (m, 9H).

Anal. $C_{16}H_{16}O_3$ (256.29) calc'd.: C 74.98; H 6.29%
found: C 75.11; H 6.10%

This compound was also prepared by Ra/Ni hydrogenation of racemic *24*.[44]

LIS Measurements

For compounds *6* and *8*, Eu(fod)$_3$ (0.008 M in $CDCl_3$) was used, and the substrate concentrations were varied in the range 0.2 M—0.05 M. A total of seven points have been used for calculation of the data.

For compound *9*, Pr(fod)$_3$ (0.008 M in CCl_4) was used, and the substrate concentration was varied in the range 0.25—0.1 M. Seven points have been used for calculation of the data.

All manipulations with reagents, solvents and compounds were carried out in a glove-box which was continuously flushed with dry nitrogen during use.

Calculations were performed on a CDC CYBER/70/720 computer. Program LISDE (Lanthanide Induced Shift DEtermination) is a revised version o fthe program already employed,[30,31] adopted for ulterior conformational studies. The minimization of the agreement factor was accomplished in two successive steps; a broad search was performed with the Monte Carlo technique[45] followed by a minimization with the SIMPLEX algorithm.[46]

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SAŽETAK

Sinteza konformacijske studije i enantioselektivna homogena katalitička hidrogenacija sa CRC-PHOSom i nekim srodnim spojevima

G. Comisso, A. Sega, V. Šunjić i A. Lisini

Lakton 1S,3R-1-hidroksi-1-difenilfosfometil-2,2,3-trimetil-ciklopentan-3-karboksilne kiseline (*8*, CRC-PHOS), te 1R,3R-bis (difenilfosfoksimetil)-2,2,3-trimetil-ciklopentan (*16*) pripravljeni su pošavši od (—)-kamfan-kiseline, odn. (—)-izo-kamforne kiseline. Njihove kompleksne soli [Rh(norbornadien)lakton [1S,3R-1-hidroksi-1-difenilfosfometil-2,3,3-trimetilciklopentan-3-karboksilne kiseline] perklorat (*27*), i [Rh (norbornadien (1R,3R)-1,2,2-trimetil-1,3-bis (difenilfosfoksimetil) ciklopentan] perklorat (*28*) izolirane su, te je njihova katalitička i enantioselektivna moć provjerena na

modelnim prokiralnim karbonskim kiselinama. Asimetrična iskorištenja su redovito bila ispod 35% enantiomernog viška (e. v.). Pokušaj priprave difosfina analognog difosfinitu *16*, tj. spoja *21*, kao i izolacija fosfinata *22*, analoga CRC-PHOS fosfinu (*8*), nije uspio. NMR LIS studija konformacija u otopini spoja *8* i modelnih spojeva *6* i *9* pokazala je da *6* i *8* posjeduju u svojoj najstabilnijoj konformaciji dihedralni kut od 165°, dok su za spoj *9* nađene dvije stabilne konformacije za kuteve 200° i 350°. Ovi rezultati ukazuju da vjerojatno nije moguće bidentatno vezanje metala preko heteroatoma X (O,P) u bočnom lancu i tetraedarskog ugljika laktonske skupine ovih spojeva.

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