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SYNTHESIS OF (+)S-α-PERFLUOROETHYL-α-HYDROXYPHENYL ACETIC ACID AND HIGHLY EFFECTIVE AUXILIARIES FOR USE IN ASYMMETRIC INDUCTION

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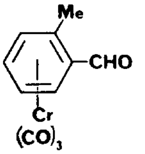
Summary : Optically pure arene-chromium-tricarbonyl alcohols 2 and 3 (readily available in both enantiomeric forms) which are powerful inducers of chirality in Prelog-type synthesis are presented. 88% optically pure (+)S- α -perfluoroethyl- α -hydroxyphenylacetic acid is synthesized for the first time in 3 steps and 73% yield.

Highly enantioselective formation of C-C bonds is of great importance in organic synthesis, but still more important is to be able to synthesize the right enantiomer. We present here two new alcohols, 2, 3, which are readily available in two enantiomeric forms from the chiral complexed aldehyde 1 and are efficient inducers of chirality on Prelog-type synthesis.



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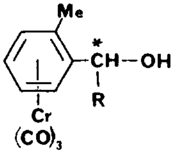
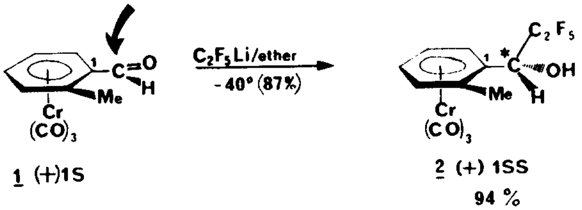


2 $R = C_2F_5 \equiv R^*_F$

3 $R = C_2H_5 \equiv R^*_H$

Addition of perfluoroethyl lithium on the complexed aldehyde 1 affords alcohols 2 with 88% of diastereomeric excess (1); ethyl-magnesium bromide affords 3 with 100% d.e. . Hence, the (+)1S and/or (-)1R complexed aldehydes 1 which are easily obtained by resolution (2), afford either alcohol 2 (+)1SS (3) and alcohol 3 (+)1SS (3,4) or the enantiomers 2 (-)1RR and 3 (-)1RR as desired, scheme 1.

Scheme 1



1 (+)1S

2 (+) 1SS
94 %

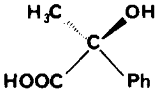
The usefulness of these chiral alcohols 2 and 3 is tested first in the Prelog asymmetric synthesis. α-Keto-esters 4, 5, 6 and 7, Table 1, have been studied.

The obtained diastereomer mixtures are analyzed by ^{1}H NMR and, when possible, by ^{19}F NMR and it appears that, in all cases, the extent of asymmetric induction is very high : 84% d.e. to almost 100% d.e. (± 3%).

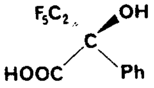
TABLE 1

R^*		R_1	R_2Met.	t°c	Yield %	d.e.%
R^*_F	4	Ph	C_2F_5Li	-40	95	89
		Ph	CH_3MgI	-70	87	86
		Ph	CH_3MgI	-100	64	92
		Ph	$C_3H_7C \equiv CMgBr$	-70	70	90
	5	Me	C_2F_5Li	-40	84	84
		Me	PhMgBr	-70	87	95
R^*_H	6	Ph	C_2F_5Li	-40	76	88
		Ph	CH_3MgI	-70	82	84
		Ph	CH_3MgI	-100	99	94
		Ph	$C_3H_7C \equiv CMgBr$	-70	70	100
	7	Me	C_2F_5Li	-40	87	90
		Me	PhMgBr	-70	92	86

Addition of methyl-Grignard on optically pure keto-ester 6 obtained from (+)1SS optically pure alcohol 3, followed by saponification gives (+)S atrolactic acid 8 ($|\alpha|^{20}_{D}$=+30.6° ± 0.3°,c=1.1,EtOH,82% ee (5)). It may thus be noted that, even with such a complexed alcohol as chiral residue, the Prelog model (7) holds and addition occurs from the rear-side as drawn on scheme 2 ($R = C_2H_5$, R_1 = Ph, $R_2 = CH_3$). Asymmetric addition of C_2F_5Li on chiral α-keto-esters is tested here for the first time. (+) α-Perfluoroethyl-α-hydroxy phenylacetic acid 9 (8) is thus obtained in high optical purity (88% ee) from keto-ester 6 in two steps and it can be predicted that the absolute configuration is S (9).



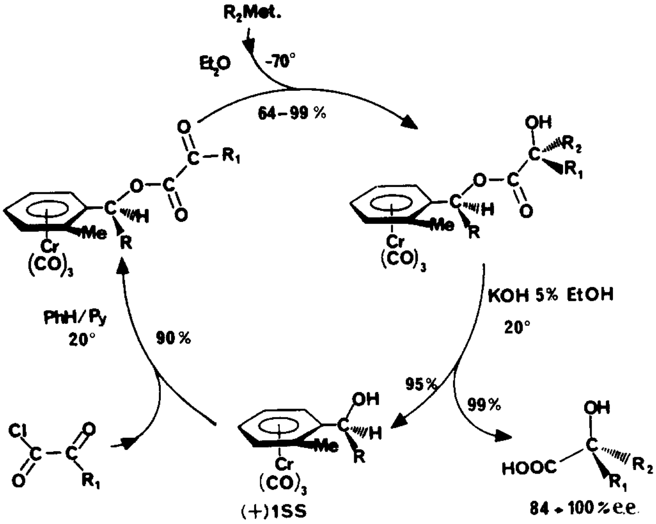
(+)S 8



(+)S 9

After saponification,the optically pure complexed alcohol (2 or 3) is recovered in 95% yield in all cases and may thus be converted again into keto-ester and used for another addition reaction as shown on scheme 2.

Scheme 2



These two new chiral alcohols appear as efficient as (-)-8-phenylmenthol during Prelog asymmetric synthesis (10,11) and are now tested on other kinds of reactions.

Acknowledgments. We thank PCUK-France for financial support and for providing pentafluoroethyl iodide.

References

(1) A. SOLLADIE-CAVALLO and J. SUFFERT, unpublished results.

(2) A. SOLLADIE-CAVALLO, G. SOLLADIE and E. TSAMO, J. Org. Chem. 44, 4189 (1979)

(3) Predominant diastereomer of alcohol 2 : yellow solid; m.p. = 94°-96°, $C_{13}H_9F_5O_4Cr$ C% calc. 41.51 Tr. 41.63, H%, Calc. 2.41 Tr. 2.42; IR($CHCl_3$) 3600 w, 3310 w, 1980 vs, 1905 vvs cm^{-1}; ^1H NMR($CDCl_3$, δ/TMS, WP 200 Bruker) 2.24(3H, s) 2.46(1H, OH, d.d. $^3J_{HH}$ = 4,5 Hz, $^3J_{HF}$ = 2Hz) 5.15(1H, d.d.d. $^3J_{HF}$ = 19Hz, $^3J_{HF}$ = 3Hz, $^3J_{HH}$ = 4.5 Hz) 5.23(1H, compl. arom. d, $^3J_{HH}$ = 6.5Hz) 5.27(1H, compl. arom., t, $^3J_{HH}$ = 6.5Hz) 5.55(1H, compl. arom.,t, $^3J_{HH}$ = 6.5Hz) 5.86(1H, compl. arom., d, $^3J_{HH}$ = 6.5Hz). ^{19}F.NMR($CDCl_3$, δ/$CFCl_3$, WH 90 Bruker) -81.95(CF_3, S) -119.13 and -131.6 (CF_2, AB system, $\Delta\nu_{AB}$ = 1050 Hz, $^2J_{AB}$ = 279 Hz). $|\alpha|_D^{20}$Max. = + 53,2° (C 0.65, $CHCl_3$). Only one diastereomer in the case of alcohol 3 : very viscous yellow oil, IR($CHCl_3$) 3600 w, 3380 w, 1970 vs, 1895 vs cm^{-1}; ^1H.NMR($CDCl_3$, δ/TMS, WP 200 Bruker) 1.02(CH_3, t) 1.65(CH_2, ABX_3, m) 1.96(OH.d) 2.15 (CH_3,s) 4.56(CH, m) 5.13(1H arom. compl.,d) 5.24(1H arom. compl.,t) 5.36(1H arom. compl., t) 5.75(1H arom. compl., d) $|\alpha|_D^{20°}$ Max. = +36° (C 0.6, $CHCl_3$)

(4) E. TSAMO, thèse d'Etat, Strasbourg, 1979

(5) (+)S atrolactic acid, IR($CHCl_3$) 3500, 3000, 1710 cm^{-1}; ^1H-NMR($CDCl_3$, δ/TMS) 1.80(3H,S) 5.75(2H, b, OH and COOH)7.32(3H, arom. m) 7.56(2H, arom. m); $|\alpha|_D^{20}$ Max = + 37.7° (c 3.5, EtOH) (6).

(6) "Tables of Resolving Agents and Optical Resolutions". S.H. WILEN, Edited by E.L. ELIEL, University of Notre Dame Press, Notre Dame, London, 1972.

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(8) α-Perfluoroethyl- α-hydroxyphenylacetic acid (+)S; mp = 93°-94°, IR($CHCl_3$) 3460, 3000, 1720 cm^{-1}; $[\alpha]_D^{20}$Max.=+5.3° ± 0.3°(C 0.9, EtOH) calculated according to the 88% d.e. measured by NMR (Table 1)

(9) (+) α-Trifluoromethyl- α-hydroxy phenyl acetic acid as been shown to be S ; L. HUB and H.S. MOSHER, J. Org. Chem. 35, 3691, 1970.

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