Highly Regio- and Stereo-selective Synthesis of 1-(2-Hydroxyaryl)glycerol Derivatives under Ultrasonic Irradiation

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Complementary diastereoselectivity in the C-arylation of (*R*)- and (*S*)-2,3-*O*-isopropylideneglyceraldehyde by using Mg^{2+}-based (*syn*-addition) and Ti^{4+}-based (*anti*-addition) phenolates allows the efficient preparation of all four possible stereoisomers of the title 1-C-substituted glycerols; the application of ultrasonic waves produces a marked synthetic advantage.

The addition of carbon centres having nucleophilic character to suitably protected glyceraldehyde derivatives represents a prominent route in asymmetric synthesis, leading to polyfunctional frameworks and biologically important targets.[1] The multifunctional nature of these popular chiral synthons, however, often results in difficult or unpredictable control of the addition mode (*syn vs. anti*) during carbon–carbon bond formation.[2] Herein we report a highly stereocontrolled synthesis of both *syn*- and *anti*-1-(2-hydroxyaryl)glycerol derivatives (**4**)—(**7**) by reaction of *in situ*-generated Mg^{2+}- and Ti^{4+}-phenolates (**1**) [ML_n = $MgBr^+$ and $Ti(OPr^i)_3^+$] with the appropriate enantiomer of 2,3-*O*-isopropylideneglyceraldehyde (**2**)[3] and (**3**)[4] under ultrasonic irradiation† (Scheme 1).

First, we investigated the reaction of (**1a**) (ML_n = $MgBr^+$) with (*R*)-glyceraldehyde acetonide (**2**) in CH_2Cl_2, magnetically stirring the resulting slurry at ambient temperature for 24 h. The reaction was only partially successful producing (**4a**) and (**5a**) in a ratio of 85 : 15 and in a disappointingly low yield of 25%. However, when subjected to ultrasonic waves[5] at 0 °C for 5 h, the same reaction mixture furnished a very high yield of the *syn* addition product (**4a**) with an improved diastereoisomeric excess (d.e.) of 92% (*syn* : *anti* ratio 96 : 4) (Table 1, entry 1). We easily extended this methodology to other magnesium phenolates and to the (*S*)-enantiomer of glyceraldehyde acetonide, (**3**), as listed in Table 1 (odd-numbered entries); in all cases the level of *syn*-stereoselection was as high as 90—93% d.e.

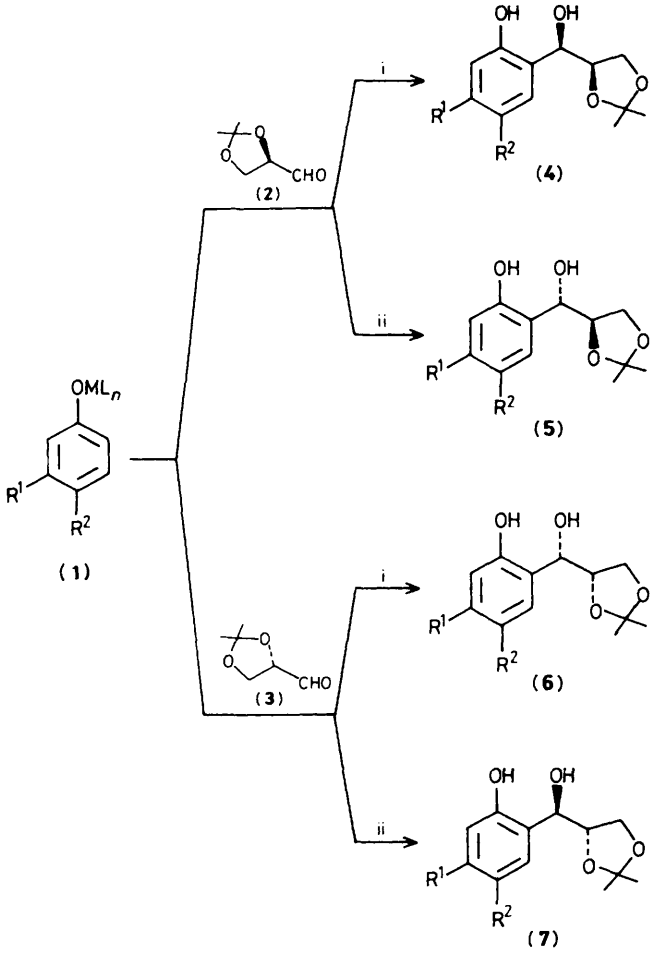
The next task was to search for conditions for stereochemistry reversal in order to obtain *anti*-addition products selectively. The target was simply reached by changing the phenolate metal counter-ion and the solvent. Thus, reactions of (**1**) [ML_n = $Ti(OPr^i)_3^+$] in toluene with (**2**) and (**3**) produced *anti*-arylglycerols (**5**) and (**7**) respectively with very high diastereoisomeric purity and good yields (even-numbered entries in Table 1).

† A Branson Type 2200 instrument (120 W, 220—240 V, 50—60 Hz) operating at a 30—50 kHz frequency was used.

Table 1. Formation of the *syn*- and *anti*-arylglycerols (**4**)—(**7**).[a]

Entry	Reactants	Counter ion (ML_n)	Product[b]	% Yield[c]	M.p./°C	$[\alpha]_D^{20}$ [d]	% D.e.[e]	Configuration
1	(**1a**) + (**2**)	$MgBr^+$	(**4a**)	70	157—158	−36.4°	92	*syn* (1*R*,2*R*)
2	(**1a**) + (**2**)	$Ti(OPr^i)_3^+$	(**5a**)	76	142—143	+43.9°	90	*anti* (1*S*,2*R*)
3	(**1b**) + (**2**)	$MgBr^+$	(**4b**)	63	[f]	−17.8°	91	*syn* (1*R*,2*R*)
4	(**1b**) + (**2**)	$Ti(OPr^i)_3^+$	(**5b**)	61	[f]	+15.4°	90	*anti* (1*S*,2*R*)
5	(**1c**) + (**2**)	$MgBr^+$	(**4c**)	76	[f]	−9.3°	93	*syn* (1*R*,2*R*)
6	(**1c**) + (**2**)	$Ti(OPr^i)_3^+$	(**5c**)	67	135 (decomp.)	+9.1°	93	*anti* (1*S*,2*R*)
7	(**1a**) + (**3**)	$MgBr^+$	(**6a**)	72	155—156	+35.6°	92	*syn* (1*S*,2*S*)
8	(**1a**) + (**3**)	$Ti(OPr^i)_3^+$	(**7a**)	75	140—141	−43.1°	91	*anti* (1*R*,2*S*)

[a] All reactions were carried out under the following typical conditions. i, Mg-based phenolates: to a solution of EtMgBr (50 mmol) in diethyl ether the appropriate phenol (50 mmol) was added; the ether was removed under vacuum and CH_2Cl_2 (200 ml) and then a solution of (**2**) or (**3**) (75 mmol) in CH_2Cl_2 (50 ml) were added at 0 °C. After sonication in a 50 kHz ultrasonic cleaning bath, usual work-up (aq. NH_4Cl quenching, extraction; drying, removal of the solvent) furnished crude *syn*-products (**4a—c**) or (**6a**) which were purified by conventional procedures. ii, Ti-based phenolates: to a solution of $Ti(OPr^i)_4$ (50 mmol) in toluene (200 ml) the appropriate phenol (50 mmol) was added; the mixture was distilled in order to remove the propan-2-ol formed azeotropically and, after cooling at 0 °C, a solution of (**2**) or (**3**) (75 mmol) in toluene (50 ml) was added. Work-up as above then furnished *anti*-products (**5a—c**) or (**7a**). [b] All compounds reported have been characterized by complete spectral and analytical data. [c] Isolated yields after crystallization (entries 1,2,7, and 8) or silica gel chromatography (entries 3—6). [d] *c* 1, benzene. [e] Diastereoisomeric excess (d.e.) assayed on the crude reaction mixtures by ^1H n.m.r. spectroscopy and reversed-phase h.p.l.c. [f] Oily substance.



a; R^1 = H, R^2 = Bu^t
b; R^1 = R^2 = H
c; R^1 = OMe, R^2 = H

Scheme 1. *Conditions:* i, ML_n = $MgBr^+$, CH_2Cl_2, ultrasound, 0 °C; ii, ML_n = $Ti(OPr^i)_3^+$, toluene, ultrasound, 0 °C.

The *syn*- and *anti*-diastereoisomeric glycerols (**4**)—(**7**) were quickly distinguished by ^1H n.m.r. spectroscopy on the basis of vicinal ^1H–^1H coupling constants as well as chemical shift values.‡ The structural assignment was corroborated by *X*-ray diffraction methods. Suitable crystals for compound (**4a**)§ were grown in diethyl ether and an ORTEP view of the molecule is shown in Figure 1. Since the configuration of C(8), which corresponds to the unaltered C-2 atom of starting (**2**), is (*R*), it can be deduced that the absolute configuration at both C(7) and C(8) (C-1 and C-2) is (*R*), the relative stereodisposition of the two chiral centres being *syn*. The torsion angle H–C(7)–C(8)–H is 177.2(4)°. The five-membered ring shows a stereochemistry half way between an envelope and a twist conformation[9] [q_2 = 0.349(6) Å; ϕ = 153.6(9)°] or, better, a twist-envelope (C_2) conformation.[10] Two short inter-

‡ Typical ^1H n.m.r. data: (**4a**) ($CDCl_3$) δ 1.27 (s, 9H, Bu^t), 1.39 (s, 3H, Me), 1.52 (s, 3H, Me), 3.34 (s, 1H, OH), 3.83 (dd, 1H, *J* 8.77 and 6.40 Hz, H-3), 3.87 (dd, 1H, *J* 8.77 and 5.12 Hz, H-3), 4.37 (ddd, 1H, *J* 8.04, 6.40, and 5.12 Hz, H-2), 4.64 (d, 1H, *J* 8.04 Hz, H-1), 6.83 (d, 1H, *J* 8.60 Hz, H-3'), 7.00 (d, 1H, *J* 2.40 Hz, H-6'), 7.23 (dd, 1H, *J* 8.60 and 2.40 Hz, H-4'), 7.80 (s, 1H, OH); (**5a**) ($CDCl_3$) δ 1.28 (s, 9H, Bu^t), 1.38 (s, 3H, Me), 1.49 (s, 3H, Me), 3.02 (s, 1H, OH), 3.96 (dd, 1H, *J* 7.97 and 6.03 Hz, H-3), 4.05 (dd, 1H, *J* 7.97 and 5.36 Hz, H-3), 4.40 (ddd, 1H, *J* 6.03, 5.36, and 4.20 Hz, H-2), 5.04 (d, 1H, *J* 4.20 Hz, H-1), 6.80 (d, 1H, *J* 8.45 Hz, H-3'), 7.03 (d, 1H, *J* 2.06 Hz, H-6'), 7.20 (dd, 1H, *J* 8.45 and 2.06 Hz, H-4'), 7.82 (s, 1H, OH).

§ *Crystal data* for (−)-(**4a**): $C_{16}H_{24}O_4$, *M* = 280.4, orthorhombic, space group $P2_12_12_1$, *a* = 12.830(1), *b* = 10.281(1), *c* = 12.209(1) Å, *U* = 1610.4 Å^3, *Z* = 4, D_c = 1.16 g cm^{-3}, *F*(000) = 608; λ = 1.54178 Å, μ (Cu-K_α) = 6.3 cm^{-1}. Intensity data were measured to $2\theta_{max.}$ = 140°, at room temperature, on a computer controlled Siemens AED by the ω–2θ scan technique. A total of 1778 reflections were measured, of which only 1300 having $I > 2\sigma(I)$ were considered observed and used in the subsequent analysis. The crystal used was 0.19 × 0.12 × 0.44 mm^3 in size. No absorption correction was applied. The structure was solved by direct methods, with MULTAN[6,7] and refined by full-matrix least-squares cycles using the SHELX-76[8] system of computer programs. The final conventional *R* index was 0.052, R_w 0.057 (observed reflections only). The hydrogen atoms were located from a Δ*F* synthesis. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

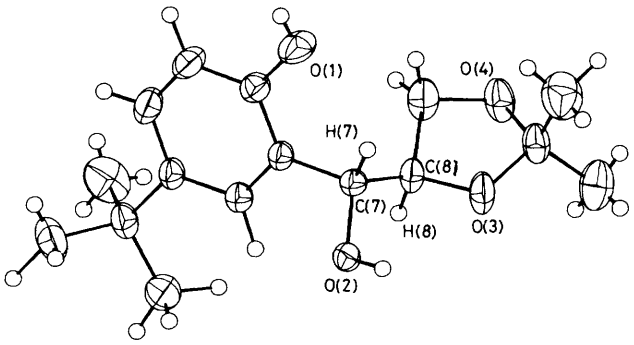


Figure 1. The molecular structure of (**4a**) showing the *syn*-stereodisposition of the two chiral centres. Thermal ellipsoids enclose 30% of probability and the hydrogen atoms are drawn with an arbitrary diameter.

molecular hydrogen bonds O(1)–H · · · O(2) (1/2 − x, y, 1/2 +z) 2.750(5) and O(2)–H · · · O(4) (x, 1/2 + y, 1/2 − z) 2.833(4) Å are present connecting the molecules in a three dimensional network. The phenolic hydroxy group lies on the mean benzene plane.

The acetonide blocked ring-hydroxylated glycerols in this study can be easily deprotected under routine conditions. Thus, for example, compounds (**4a**) and (**5a**) upon treatment with acetic acid–water 1 : 2 mixture (room temp., 12 h) were converted into *syn*- and *anti*-1-(2-hydroxy-5-t-butylphenyl)-1,2,3-trihydroxypropane quantitatively with conservation of the enantiomeric integrity.

In summary, we have provided an efficient way of controlling phenol addition to either diastereoface of (**2**) and (**3**). By extension of these results, the use of higher glyceraldehyde homologues or aldehydo sugar derivatives should provide a promising entry into new chiral alditols bearing ring-hydroxylated aromatic appendages.

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