J. CHEM. SOC., CHEM. COMMUN., 1987

## 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<sup>4+</sup>-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.<sup>1</sup> 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.<sup>2</sup> 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<sup>2+</sup>- and Ti<sup>4+</sup>-phenolates (1) [ML<sub>n</sub> = MgBr<sup>+</sup> and Ti(OPri)<sub>3</sub><sup>+</sup>] with the appropriate enantiomer of 2,3-O-isopropylideneglyceraldehyde (2)<sup>3</sup> and (3)<sup>4</sup> under ultrasonic irradiation<sup>+</sup> (Scheme 1).

First, we investigated the reaction of (1a) ( $ML_n = MgBr^+$ ) with (*R*)-glyceraldehyde acetonide (2) in CH<sub>2</sub>Cl<sub>2</sub>, 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<sup>5</sup> 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 glyceral-dehyde 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).

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<sup>†</sup> 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).<sup>a</sup>

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

<sup>a</sup> 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<sub>4</sub>Cl 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(OPri)<sub>4</sub> (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). <sup>b</sup> All compounds reported have been characterized by complete spectral and analytical data. <sup>c</sup> Isolated yields after crystallization (entries 1,2,7, and 8) or silica gel chromatography (entries 3—6). <sup>d</sup> c 1, benzene. <sup>e</sup> Diastereoisomeric excess (d.e.) assayed on the crude reaction mixtures by <sup>1</sup>H n.m.r. spectroscopy and reversed-phase h.p.l.c. <sup>f</sup> Oily substance.



а;	$\mathbf{K}^{\prime} = \mathbf{\Pi}, \mathbf{K}^{\prime} = \mathbf{D}\mathbf{u}^{\prime}$
b;	$\mathbf{R}^1 = \mathbf{R}^2 = \mathbf{H}$
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 <sup>1</sup>H n.m.r. spectroscopy on the basis of vicinal <sup>1</sup>H–<sup>1</sup>H 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<sup>9</sup> [ $q_2 = 0.349(6)$  Å;  $\phi = 153.6(9)^\circ$ ] or, better, a twist-envelope ( $C_2$ ) conformation.<sup>10</sup> Two short inter-

‡ Typical <sup>1</sup>H n.m.r. data: (4a) (CDCl<sub>3</sub>)  $\delta$  1.27 (s, 9H, Bu<sup>1</sup>), 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 (dd, 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<sub>3</sub>)  $\delta$  1.28 (s, 9H, Bu<sup>1</sup>), 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 6.43, 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<sub>16</sub>H<sub>24</sub>O<sub>4</sub>, 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<sup>3</sup>, Z = 4,  $D_c$  = 1.16 g cm<sup>-3</sup>, F(000) = 608;  $\lambda$  = 1.54178 Å,  $\mu$  (Cu- $K_{\alpha}$ ) = 6.3 cm<sup>-1</sup>. Intensity data were measured to  $2\theta_{max} = 140^{\circ}$ , at room temperature, on a computer controlled Siemens AED by the  $\omega$ -2 $\theta$  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  $0.19 \times 0.12 \times 0.44$ mm<sup>3</sup> in size. No absorption correction was applied. The structure was solved by direct methods, with MULTAN6.7 and refined by fullmatrix least-squares cycles using the SHELX-768 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  $\Delta F$  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.

Published on 01 January 1987. Downloaded by Universitat Politècnica de València on 27/10/2014 22:31:23

We gratefully acknowledge support by the Ministero della Pubblica Istruzione.

Received, 5th November 1986; Com. 1581

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0(1)

H(7)

0(4)

O(3)

H(8)

molecular hydrogen bonds  $O(1)-H \cdots O(2)$  (1/2 - x, y, 1/2 + z) 2.750(5) and  $O(2)-H \cdots O(4)$  (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.

diameter.