

Mutual Kinetic Resolution in Aldol Condensation between 2-Phenylpropanal and 4,5-Dihydro-5-methyl-2-(trimethylsiloxy)-3-(trimethylsilyl)furan

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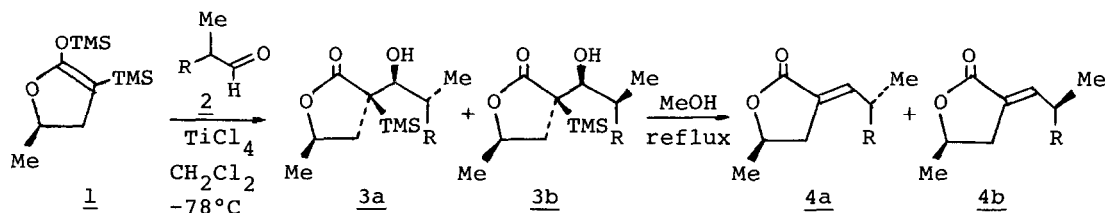
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Summary: The titanium(IV) chloride-mediated aldol condensation between title compounds proceeds with high diastereoselectivity (Cram) to give 3a exclusively (99% purity).

The aldol condensation of a chiral aldehyde with a geometrically well defined chiral enolate may result in consonant double stereodifferentiation to form one diastereomer selectively from possible eight diastereomers (dl pair). The most important property that the chiral enolate must have is an inherent diastereofacial preference in its reaction with an achiral aldehyde. A remarkable enhancement of the 1,2-diastereoselectivity (usually Cram)¹⁾ is then observed in a reaction of this enolate with an α -chiral aldehyde which exhibits rather poor inherent diastereofacial preference. This phenomenon is recognized as a double stereodifferentiation with mutual kinetic resolution.²⁾

In a previous paper, we have demonstrated a complete diastereoselectivity of titanium(IV) chloride-mediated aldol condensation between 4,5-dihydro-5-methyl-2-(trimethylsiloxy)-3-(trimethylsilyl)furan (1) and achiral aldehydes.³⁾ In this reaction, 1 shows the excellent inherent diastereofacial preference (both threo and 1,3-trans) to form one diastereomer of four possible ones. Therefore, it is anticipated that when this reaction is carried out with an α -chiral (racemic) aldehyde instead of achiral aldehyde, we can observe consonant double stereodifferentiation between a matched pair. We wish to describe herein this is the case with mutual kinetic resolution in the reaction of (\pm)-1 with (\pm)-2-phenylpropanal (2) (Scheme 1 : R = Ph).

Scheme 1 (R = Ph or Et)



The aldol condensation of (\pm)-1 (3.67 g, 15 mmol) with (\pm)-2 (2.7 mL, 20 mmol, 1.3 equiv) was carried out in the presence of TiCl_4 (2.2 mL, 20 mmol, 1.3 equiv) at -78°C in CH_2Cl_2 (40 mL) for 1 h. The mixture was quenched with MeOH followed by aqueous work-up and organic material was extracted (CH_2Cl_2) to give crude ($2'R^*S^*,1'S^*,3R^*,5R^*$)-4,5-dihydro-5-methyl-3-{2'-phenyl-1'-(hydroxypropyl)}-3-(trimethylsilyl)-2(3H)furanone ((\pm)-3)⁴) (2.86 g, 62.2%) as white needles. The diastereomeric purity of 3 was hard to determine at this stage even by consistent spectrum of ^1H NMR (400 MHz) because of its complexity. In this reaction, however, it is certain that 1 shows an excellent threo selectivity. The aldol product (\pm)-3 was then converted by β -elimination of trimethylsilanol into (*E*)-(\pm)- α -{2'-(phenylpropylidene)}- γ -valerolactone, (\pm)-4, to determine the relative configurations at C-5 vs C-2' in 4. The elimination of (\pm)-3 was performed under refluxing methanol⁵) to give (\pm)-4 (quantitative). ^1H NMR (400 MHz) of (\pm)-4 indicated a trace of an epimer. The ratio of ($2'S^*,5R^*$)-4a and ($2'R^*,5R^*$)-4b was found to be 99 : 1 on the basis of GLC analysis (base-line separation by a capillary column Silicone OV-1, 30 m at 140°C).

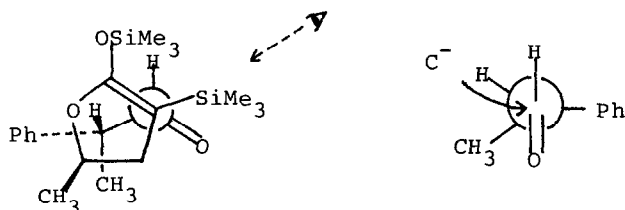


Figure 1

The result clearly demonstrates that a remarkably high 1,2-diastereoselection (Cram) of 2 operates during the reaction despite a moderate inherent diasterofacial preference of 2.²⁾ (vide infra): On the basis of extended acyclic transition states, it is assumed that (*R*)-1 reacts much faster with (*R*)-2 than with (*S*)-2 (Fig. 1). In order to confirm the absolute configurations at C-5 and C-2' in 4, optically pure (*R*)-(+)- γ -valerolactone⁶⁾ was used in the present sequence of reactions. Thus, optically pure (*R*)-(+)-1 was prepared by a usual manner⁷⁾ in 75% yield ($[\alpha]_D^{25} +16.9^\circ$ (c 1.97, CH_2Cl_2)). The aldol condensation with (\pm)-2 (3 equiv) gave ($2'R,1'S,3R,5R$)-(+)-3 ($[\alpha]_D^{25} +43.2^\circ$ (c 0.81, CH_2Cl_2)) as white needles (53-64% yield)⁸⁾. The crude (+)-3 was converted to (+)-4 by the method described above (95% yield). GLC analysis revealed the ratio of ($2'S,5R$)-(+)-4a⁹⁾ and ($2'R,5R$)-(-)-4b^{10,11)} to be 95 : 5 ($[\alpha]_D^{25} +133.7^\circ$ (c 1.03, CH_2Cl_2)). The epimeric mixture of 4 was subjected to ozonolysis followed by immediate NaBH_4 reduction to give (*R*)-(+)-2-phenylpropanol (78% yield).¹²⁾ Therefore, it is firmly evidenced that (*R*)-1 reacts with (*R*)-2 with almost exclusion of (*S*)-2.

In contrast to the high diastereoselectivity with 2, reaction of (\pm)-1 with (\pm)-2-methylbutanal showed rather blunt selectivity, the ratio of (\pm)-3a and (\pm)-3b being 3 : 1 determined by ^1H NMR (Scheme 1 : $R = \text{Et}$, 96% yield).¹³⁾

In conclusion, we have observed an interesting instance of mutual kinetic resolution in the reaction of (\pm)-1 with (\pm)-2 (R = Ph) to form (\pm)-3a in greater preference over (\pm)-3b (99 : 1). It has been argued²⁾ that in the aldol condensation involving two chiral components, the magnitude of mutual kinetic resolution depends upon the respective inherent diastereofacial preference shown by the two reactants in their reactions with achiral reaction partners. In the present reaction, racemic 1 reacts with isobutyraldehyde (achiral analog of 2) to give only one diastereomer¹⁴⁾ in 90% yield. On the other hand, 4,5-dihydro-2-(trimethylsiloxy)-3-(trimethylsilyl)furan (achiral analog of 1) reacts with racemic 2 (R = Ph) to give a diastereomeric mixture in a ratio of 9 : 1 (76% yield).¹⁵⁾ Therefore, the inherent diastereoselectivity of 2 was greatly enhanced by a factor of ten in the reaction with 1 by advantageous face-matching. The reason of this highly consonant double stereodifferentiation must stem from the geometrically pure (Z)-enol of the lactone ring which bears a methyl group blocking one face of the ring.¹⁶⁾

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- 2) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S.D. Young, and J. E. Sohn, *J. Am. Chem. Soc.*, **101**, 7077 (1979). C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, and S. D. Young, *J. Org. Chem.*, **46**, 2290 (1981). See also C. H. Heathcock, "Asymmetric Synthesis", J. D. Morrison, Ed., Vol 3, Academic Press (1984), pp 165-212 and references cited therein.
- 3) K. Yamamoto and Y. Tomo, *Chem. Lett.*, 531 (1983).
- 4) ¹H NMR(CDCl₃) : δ 0.161 (s, 9H, Si(CH₃)₃), 1.319 (d, J = 6.23 Hz, 3H, CH₃CO), 1.373 (d, J = 6.96 Hz, 3H, CH₃-C-Ph), 1.695 (dd, J = 8.13, 14.28 Hz, 1H, HCH), 2.122 (br, 1H, OH), 2.688 (dd, J = 8.35, 14.28 Hz, 1H, HCH), 2.986 (quintet, J = 6.60 Hz, 1H, CH-Ph), 4.288 (ddq, J = 6.23, 8.13, 8.35 Hz, 1H, OCH), 4.386 (br d, J = 5.86 Hz, 1H, HOCH), 7.0 - 7.3 (m, 5H, aromatic proton) ; ¹³C NMR(CDCl₃) : δ -2.5, 17.6, 22.0, 32.7, 44.2, 46.1, 74.9, 77.6, 126.9, 127.9, 128.6, 143.8, 179.6 ; IR (Nujor) : 3440, 1710, 1250, 840 cm⁻¹ ; mp 139.7 - 140.8°C.
- 5) Under basic Peterson olefination conditions, such as KH in THF, resulting (\pm)-4 was easily isomerized to α -{2'-(phenylpropenyl)}- γ -valerolactone. The latter was isomerized again in methanolic NaOMe to give a mixture of 4a and 4b (7:3 by GLC analysis).
- 6) (R)-(+)- γ -Valerolactone was prepared by literature procedures from L-glutamic acid ; M. Taniguchi, K. Koga and S. Yamada, *Tetrahedron*, **30**, 3547

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- 7) K. Yamamoto, Y. Tomo, and S. Suzuki, Tetrahedron Lett., 21, 2861 (1980).
- 8) mp 145.2 - 145.7°C ; $[\alpha]_D^{25} +48.7^\circ$ (c 0.82, CH₂Cl₂) obtained from recrystallized sample (hexane : ether : CH₂Cl₂ = 7 : 1.5 : 5).
- 9) (2'S,5R)-(+)-4a : ¹H NMR(CDCl₃) : δ 1.384 (d, J = 6.23 Hz, 3H, CH₃-CO), 1.423 (d, J = 6.96 Hz, 3H, CH₃-CPh), 2.437 (ddd, J = 2.93, 5.86, 16.85 Hz, 1H, HCH), 2.930 (ddd, J = 2.56, 7.69, 16.85 Hz, 1H, HCH), 3.585 (dq, J = 6.96, 9.16 Hz, CHCPh), 4.579 (ddq, J = 5.86, 7.69, 6.22 Hz, 1H, OCH), 6.860 (td, J = 2.93, 9.53 Hz, 1H, olefinic proton), 7.1 - 7.3 (m, 5H, aromatic proton) ; ¹³C NMR(CDCl₃) : δ 21.3, 22.2, 32.8, 40.6, 73.9, 125.8, 126.8, 126.9, 128.7, 143.5, 143.8, 170.9 ; IR(neat) : 1750, 1680 cm⁻¹ ; $[\alpha]_D^{25} +150.0^\circ$ (c 0.73, CH₂Cl₂).
- 10) In another run, the reaction of (R)-(+)-1 with an equimolar amount of (±)-2 was carried out to give a significant amount of epimer 3b. As a result the elimination product (-)-4b was found to form in competition with (+)-4a in a ratio of ca. 3:7, the former being isolated in a pure state by HPLC.
- 11) (2'R,5R)-(-)-4b : ¹H NMR(CDCl₃) : δ 1.355 (d, J = 6.37 Hz, 3H, CH₃-CO), 1.430 (d, J = 7.14 Hz, 3H, CH₃-CPh), 2.303 (ddd, J = 2.80, 5.55, 16.92 Hz, 1H, HCH), 3.030 (ddd, J = 2.64, 7.69, 16.92 Hz, 1H, HCH), 3.590 (dq, J = 7.18, 9.34 Hz, 1H, CHCPh), 4.645 (ddq, J = 5.55, 7.69, 6.37 Hz, 1H, OCH), 6.859 (td, J = 2.86, 9.34 Hz, 1H, olefinic proton), 7.1 - 7.3 (m, 5H, aromatic proton) ; ¹³C NMR(CDCl₃) : δ 21.4, 22.2, 32.9, 40.6, 74.0, 125.8, 126.8, 127.0, 128.8, 143.4, 143.8, 171.0 ; IR(neat) : 1750 1675 cm⁻¹ ; $[\alpha]_D^{25} -86.2^\circ$ (c 0.29, CH₂Cl₂).
- 12) (R)-(+)-2-Phenylpropanol was isolated with only 17% ee, presumably due to extensive racemization of intermediate 2-phenylpropanal.
- 13) ¹H NMR(CDCl₃) : δ 1.395 (d, J = 6.16 Hz, minor isomer), 1.417 (d, J = 6.15 Hz, major isomer).
- 14) (1'R*,3S*,5S*)-4,5-Dihydro-5-methyl-3-{2'-methyl-1'-(hydroxypropyl)}-3-(trimethylsilyl)-2(3H)furanone ; ¹H NMR(CDCl₃) : δ 0.160 (s, 9H, Si(CH₃)₃), 0.895 and 1.025 (each d, J = 6.60 Hz, 6H, (CH₃)₂C), 1.422 (d, J = 6.15 Hz, 3H, CH₃CO), 1.726 (dd, J = 8.57, 14.28 Hz, 1H, HCH), 1.5 - 2.1 (m, J = 6.60 Hz, 1H, Me₂CH), 2.365 (d, J = 5.94 Hz, 1H, OH), 2.650 (dd, J = 8.13, 14.29 Hz, HCH), 3.835 (dd, J = 6.15, 7.69 Hz, 1H, HO-CH), 4.622 (ddq, J = 8.13, 8.35, 6.15 Hz, 1H, OCH) ; ¹³C NMR(CDCl₃) : δ -2.6, 19.5, 20.5, 22.0, 32.7, 45.7, 75.3, 79.2, 180.5 ; IR (Nujor) : 3400, 1710, 1250, 845 cm⁻¹ ; mp 118.9 - 119.8°C.
- 15) (2'R*,1'S*,3R*)-4,5-Dihydro-3-{2'-phenyl-1'-(hydroxypropyl)}-3-(trimethylsilyl)-2(3H)furanone ; ¹H NMR(CDCl₃) : δ 0.191 (s, Si(CH₃)₃, major isomer), 0.260 (s, Si(CH₃)₃, minor isomer), 1.304 (d, J = 7.0 Hz, CH₃, minor isomer), 1.383 (d, J = 7.0 Hz, CH₃, major isomer) ; IR (Nujor) : 3480, 1715, 1250, 840 cm⁻¹ ; mp 134.2 - 134.8°C.
- 16) All melting points were recorded with recrystallized samples and all new products gave satisfactory elemental analyses.

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