Tetrahedron Letters,Vol.27,No.14,pp 1533-1536,1986
Printed in Great Britain
0040-4039/86 $3.00 + .00
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A *MESO* SPECIFIC REACTION

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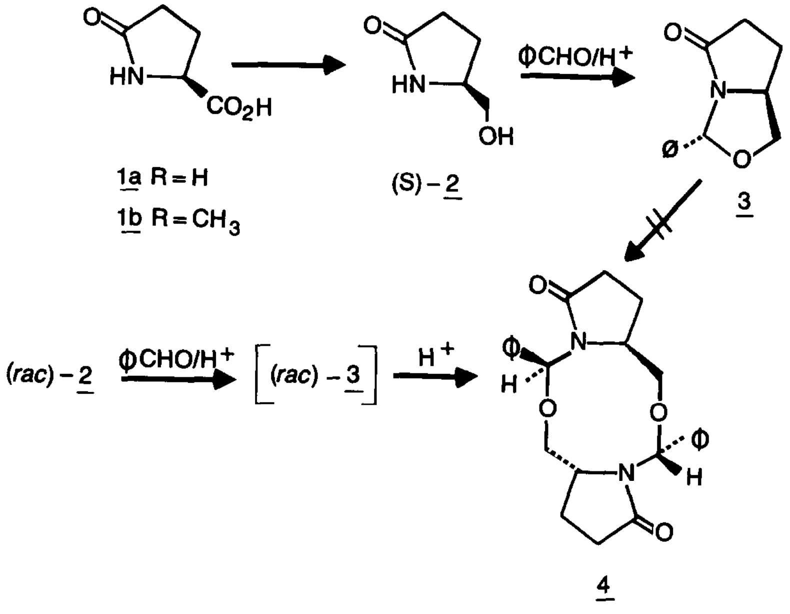
Summary: Acid–catalyzed condensation of optically pure 5–(hydroxymethyl)–2–pyrrolidinone, 2, with benzaldehyde gives only a monomeric optically active oxazolidine, 3, while under the same conditions, racemic 2 gives only a *meso* centrosymmetric compound 4 – a dimer of racemic 3. This *meso* specific reaction serves as a highly efficient method for increasing the optical purity of the generally useful chiral building blocks 2 and 3.

In the course of preparing large amounts of optically active 3 from the known amide alcohol 2,[1] prepared from commercial sources of (S)–pyroglutamic acid, we obtained varying amounts of an interesting side product 4.



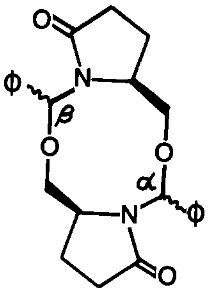
Although 4 and the desired 3 show similar NMR absorptions,[2] 3 is an optically active ($[\alpha]_D$ = +269.6°, c=1, $CHCl_3$) liquid (mp <25°), while 4 is an optically inactive crystalline material (mp >285°) which is practically insoluble in most common laboratory solvents.

The molecular structure of 4 was determined by single crystal X−ray analysis and found to be a centrosymmetric *meso* "dimer" of 3 derived from both (S)−2 and (R)−2. It was clear that 4 must have been formed from some racemic 2 as a contaminant, for, as expected, optically pure 2 was found to give optically pure 3, with no evidence for racemization or the formation of 4, under identical reaction conditions. Moreover, totally racemic solutions of the alcohol 2 could be converted quantitatively to the *meso* dimer 4 under identical reaction conditions. Racemic 3, isolated at early stages of the reaction of racemic 2, was also shown to dimerize quantitatively to 4 upon further treatment with the acid catalyst.

Especially striking in all of these studies of the chemical intermediates and products of the reactions was the absence of any detectable amounts of chiral dimers 5a−c analogous to 4 but derived from two 5−(hydroxymethyl)−2−pyrrolidinone moieties of the same absolute configuration.

The diastereoselectivity of the acid catalyzed dimerization has quite striking ramifications: *racemic solutions of reactants undergo chemical transformation whereas optically pure solutions are inert under the same conditions.* In practice, this racemic selective dimerization serves as a convenient and efficient method for the optical purification of 3 (and 2) in that all, and only, racemic combinations of reactants are further transformed to a dimeric structure (4).

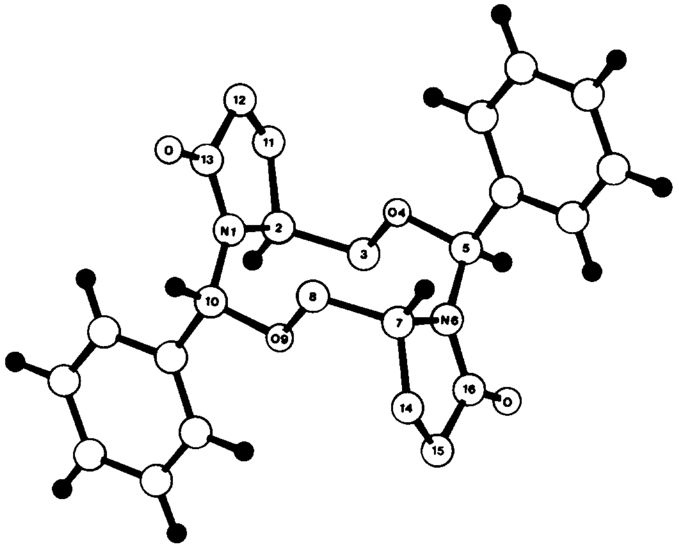
The above example of a *meso specific* reaction in which only *meso* but not racemic products are formed from racemic reactants appears to be unusual.[3] High *meso* specificity reflects a strong preference for the combination of reactants of different absolute configuration. An example of the opposite type of specificity in which only reactants of the same absolute configuration combine during reaction was recently described by Paquette *et al.*[4]



Structure	absolute configuration Cα	Cß	ΔH_f° (calc. kcal/mole)
5a	R	R	−77.4
5b	S	S	−74.2
5c	R	S	−71.4
4	*(meso)*		−85.9

We have carried out MNDO calculations[5] in which the coordinates of all atoms of each diastereomer (4, 5a−c) were optimized so as to minimize the potential energy to within ±0.3 kcal. These calculations suggest that the observed product 4 is 8.5, 11.7, and 14.5 kcal/mole more stable than the experimentally unobserved dimers 5a−c, respectively.

The ten−membered ring of 4 in the solid state exists in a boat−chair−boat conformation[6] in which the phenyl rings and carbonyl groups occupy pseudo−axial positions while the methylene groups (C11, C14), of the pyrrolidinone moieties occupy pseudo−equatorial positions.



The calculated (gas–phase) conformation of 4 is in reasonable agreement with the experimentally observed structure:

Torsional Angles (°)

Structure	1	2	3	4	5	6	7	8	9	10
4(obs)	−52	162	−69	−66	66	52	−162	69	66	−66
4(calc)	−52	160	−72	−67	65	46	−157	70	69	−61
5a	−39	174	−138	47	−59	96	−161	68	70	−60
5b	−55	163	−79	7	−61	143	−69	−46	121	−66
5c	100	−162	71	63	−58	−55	163	−122	57	−59

*Angle code: (1) C10–N1–C2–C3; (2) N1–C2–C3–O4; (3) C2–C3–O4–C5; (4) C3–O4–C5–N6; (5) O4–C5–N6–C7; (6) C5–N6–C7–C8; (7) N6–C7–C8–O9 (8) C7–C8–O9–C10; (9) C8–O9–C10–N1; (10) O9–C10–C1–C2.

These macrocyclic torsional angles for the calculated structures of the diastereomeric dimers 5a–c represent boat–chair–chair, intermediate, and boat–chair–chair conformations, respectively.

Acknowledgment: We thank Drs. C. M. Cimarusti, J. L. Moniot, R. H. Mueller, and F. L. Weisenborn for their interest in this work and Dr. M. A. Porubcan and The Squibb Institute Analytical Department for assistance during the course of this work.

References and Notes

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2. a) ^{13}C NMR (15 MHz INEPT) data: 3, ($CDCl_3$): δ 177.46 (C_{13}); 138.43 (Ar−C); 127.78 and 125.32 (AR−CH's); 86.42 (C_{10}); 70.96 (C_3); 58.17 (C_2); 32.71 (C_{12}) and 22.25 (C_{11}). 4, ($CDCl_3$): δ 177.72 (C_{13},C_{16}); 136.94 (Ar−C's); 128.69, 128.50 and 126.03 (Ar−CH's); 80.38 (C_5,C_{10}); 68.43 (C_3,C_8); 54.92 (C_2,C_7); 30.89 (C_{12},C_{15}) and 22.38 (C_{11},C_{14}).
   b) Partial ^{1}HNMR (400 HMz) data: 3, ($CDCl_3$): δ 6.34 (1H,S); 4.22 (1H,dd,J=8.0 & 6.4 Hz); 4.20−4.12 (1H,m); 3.48 (1H,t,J=8.0 Hz); 2.85−2.76 (1H,m); 2.41−2.33 (1H,m) and 1.98−1.89 (1H,m). 4, ($CDCl_3$);δ6.58 (1H,s); 4.18 (1H,dd,J=9.5 & 3.0 Hz); 3.50−3.45 (2H,m); 2.86−2.77 (1H,m); 2.53−2.45 (1H,m and 2.13−2.07 (2H,m).
3. Self−condensation of racemic amino acid derivatives, for example, leads to both *meso* and racemic diketopiperazines. See A. Ohta *et al.*, *J. Heterocyclic Chem.*, 19, 781 (1982).
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(Received in USA 28 October 1985)