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Optical Resolution of *alltrans*-2,3,4,5-Tetramethylcyclopentanone and Determination of the Configuration of the Laevorotatory Enantiomer

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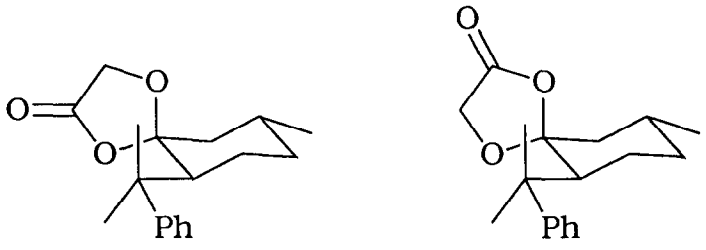
Key Words: (-)-(2R,3S,4S,5R)-Tetramethylcyclopentanone, (+)-(2R,3S,4S,5R)-Tetramethylcyclopentanol, C_2-Symmetry, Chiral induction, Dioxole

Abstract *- alltrans-2,3,4,5-Tetramethylcyclopentanone* **4** *is reduced to the corresponding alcohol* **5**. *The optical resolution of* **5** *was carried out by using the phthalate halfester method. The configuration of (-)-*__4__ *is determined by CD. The possibility of the application as a chiral auxiliary is demonstrated.*

Chiral ketones are frequently used as chiral auxiliaries in diastereoselective synthesis.[1,2,3] By using asymmetric ketones in the dioxolanone synthesis (eg. according to Pearson[1]), the formation of two diastereomers is observed (Scheme 1). They have to be separated, since one of them gives opposite side differentiation of the other in the subsequent alkylation reaction.

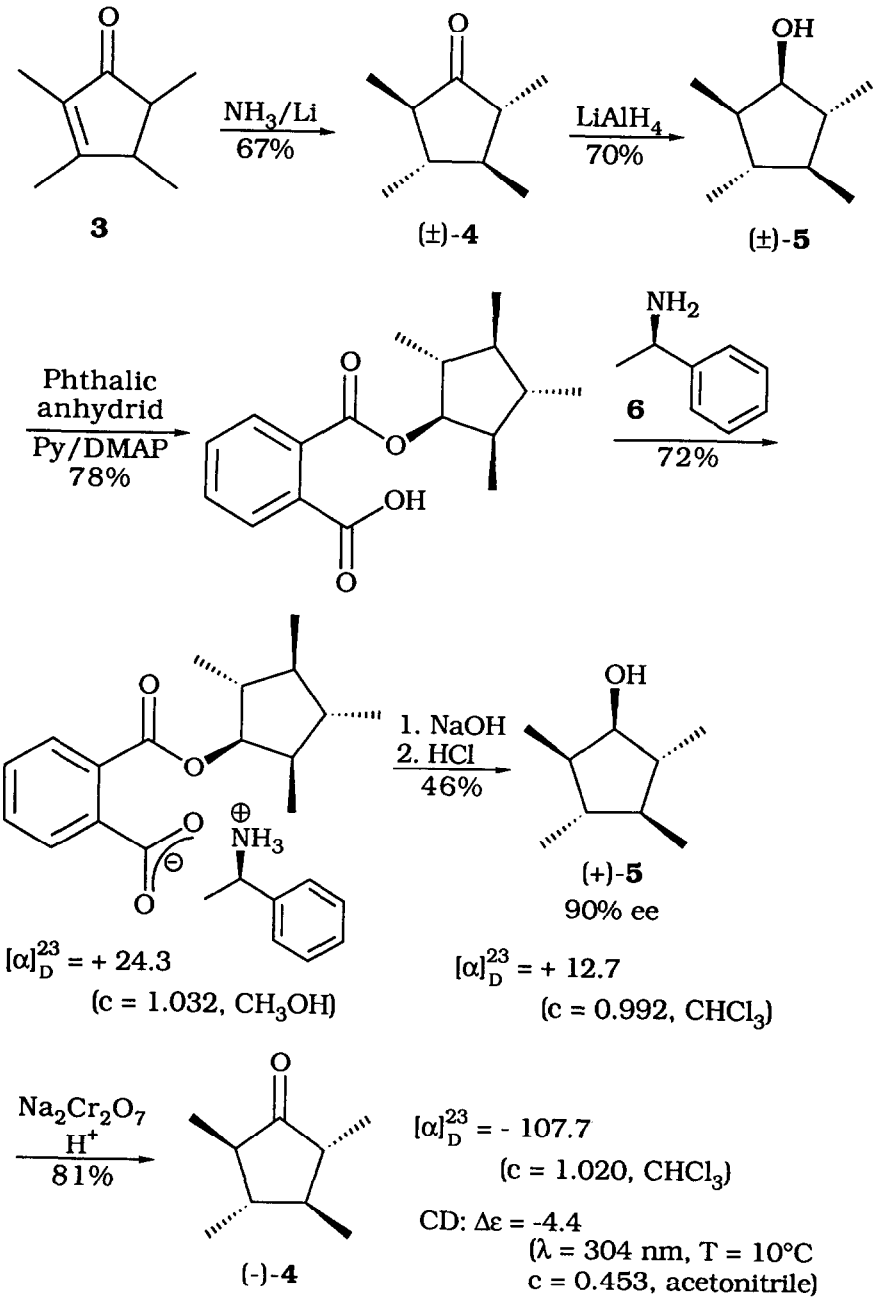


Scheme 1

This problem can be avoided by introducing a chiral C_2-symmetric ketone. In this case the formation of only one dioxolanone is possible. Some chiral C_2-symmetric ketones are described in the literature.[4] Unfortunately nature doesn't offer such compounds from the chiral pool.[3]

We present the optical resolution of *alltrans*-2,3,4,5-tetramethylcyclopentanone **4** and the configuration of the leavoratory enantiomer is determined. While our work was in progress, Sorensen and Whitworth[5] published the racemic synthesis of **4**.

The well known 2,3,4,5-tetramethylcyclopentene-2-one **3**[6] is reduced by Li/NH_3 (Scheme 2). This method favors the

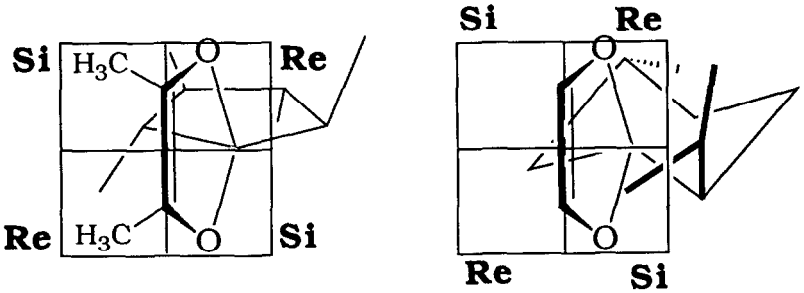

O
NH3/Li
67%
O
LiAlH4
70%
OH
3
(±)-4
(±)-5
Phthalic
anhydrid
Py/DMAP
78%
O
O
OH
O
NH2
6
72%
O
O
O
⊖
⊕
NH3
1. NaOH
2. HCl
46%
OH
(+)-5
90% ee
[α]D23 = + 24.3
(c = 1.032, CH3OH)
[α]D23 = + 12.7
(c = 0.992, CHCl3)
Na2Cr2O7
H+
81%
O
(-)-4
[α]D23 = - 107.7
(c = 1.020, CHCl3)
CD: Δε = -4.4
(λ = 304 nm, T = 10°C
c = 0.453, acetonitrile)

Scheme 2

formation of the thermodynamic diastereomer **4** (*alltrans*-Isomer).[13]

The ketone is further reduced with $LiAlH_4$ to get the tetramethylpentanol **5**. The optical resolution of this alcohol is carried out by using the halfester method.[7] R-(+)-Phenylethylamine **6** is used as base. The ammonium salt **7** is precipiated and recrystallized twice from acetone. Its decompositon yields the dextrortatory enantiomer of the the alcohol **5** with 90% ee (determined by Mosher's method[8]. The oxidation of **5** with $Na_2Cr_2O_7$ is carried out in a acidic two phase system H_2O/ether. In this way the laevorotatory enantiomer of *alltrans*-2,3,4,5-tetramethylcyclopentanone **4** is obtained. It has negative circular dichroism for the $n\pi^*$-excitation. The application of the octant rule as well as comparison with the circular dichroism of chiral cyclopentanones of known absolute configuration[9] leads to the conclusion, that the configuration of (-)-*alltrans*-2,3,4,5-tetramethylcyclopentanone **4** is 2*R*, 3*S*, 4*S*, 5*R*.

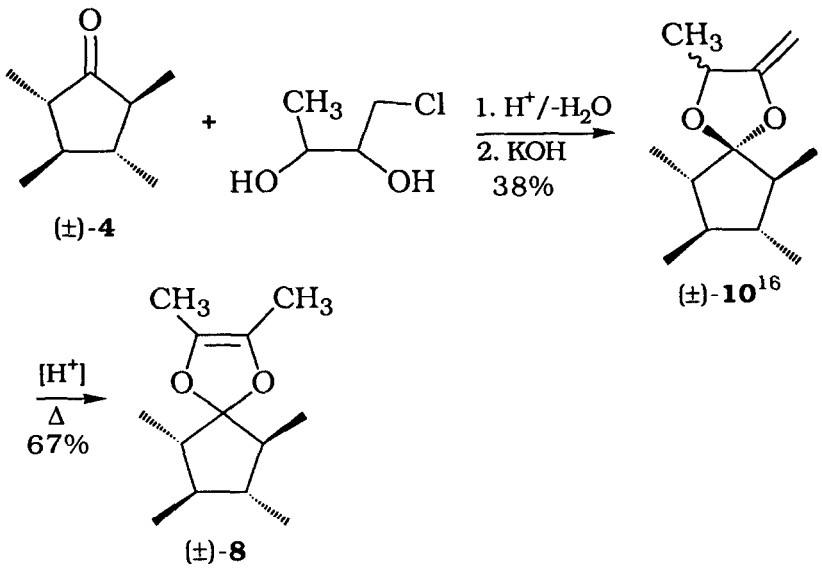
This ketone is also suitable for chiral induction in C_{2v}-symmetric prochiral units, eg. *cis*-dienol part of **8**. In this case the formation of only two diastereomers is possible, if one new asymmetric center is created. This is due to the existence of a C_2-axis in the molecule **8** (differentiation of two quadrants) (Scheme 3). By application of normal side differentiation the two enantiomers are obtained after removal of the asymmetric chiral auxiliary because of H/T-Isomerism **9**.



8 **9**[11]

Scheme 3

The compound (±)-**8**[15] is synthesized from (±)-**4** according the procedure published earlier[12] (Scheme 4).



(±)-**4** (±)-**10**[16]

(±)-**8**

Scheme 4

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13. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.65 (d/d, J = 10.7/7.0 Hz, 2 H), 1.22 (m, 2 H), 1.13 (d, broaden, J = 5.4 Hz, 6 H), 1.08 (d, J = 7.0 Hz, 5 H) ppm - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 221.51, 51.30, 45.27, 16.44, 12.87 ppm.
14. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.63 (d/d, J = 4.7/7.0 Hz, 1 H), 2.35 (s, broad, 1 H), 1.46 (d/p, J = 10.0/7.0 Hz, 1 H), 1.34 (d/d/q, J = 5.0/9.0/7.0 Hz, 1 H), 1.14 (m, 1 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H) ppm - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 81.23, 50.17, 47.90, 47.03, 44.72, 17.86, 17.22, 17.14, 12.78 ppm.
15. ^{1}H-NMR (300 MHz, C_6D_6): δ = 1.66 (d/q, J = 7.0/10.0 Hz, 2H), 1.61 (s, 6H), 1.11 (d, J = 7.0 Hz, 6H), 1.0 (m, 2H), 0,90 (d, broaden, J = 5.7 Hz, 6H) ppm - ^{13}C-NMR (75 MHz, C_6D_6): δ = 128.22, 120.25, 50.37, 46.28, 17.15, 13.11, 9.34 ppm.
16. ^{1}H-NMR (300 MHz, C_6D_6, mixture of two diastereomers): δ = 4.50 (m), 4.35 (m), 3.68 (m), 1.50 - 1.70 (m), 1.24 (d, J = 6.0 Hz), 1.22(d, J = 6.0 Hz), 0.82 - 1.12 (m) ppm - ^{13}C-NMR (75 MHz, C_6D_6, mixture of two diastereomers): δ = 162.25, 161.97, 119.78, 118.96, 76.45, 76.29, 73.83, 73.26, 50.30, 49.62, 49.29, 48.07, 47.07, 45.81, 45.67, 20.33, 19.86, 17.35, 17.06, 16.88, 14.77, 14.28, 12.28, 11.28 ppm.