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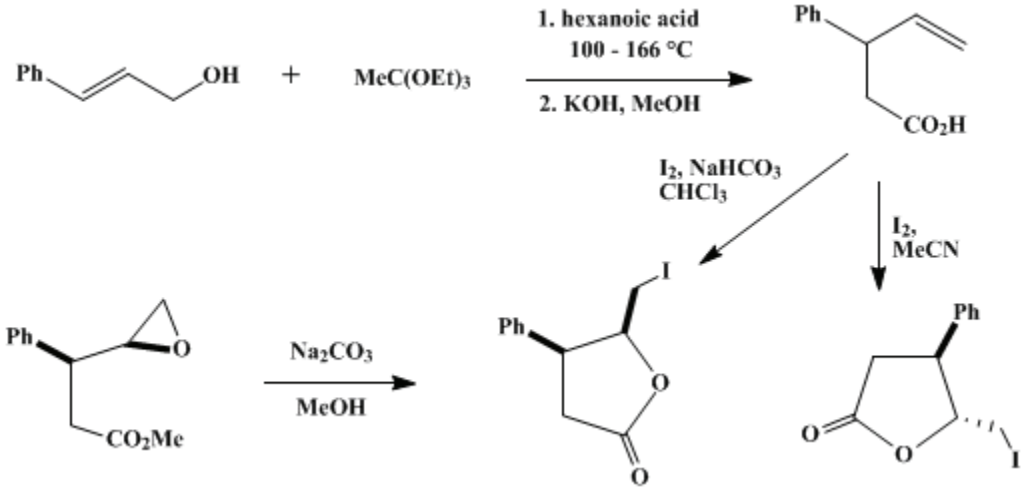
STEREOCONTROLLED IODOLACTONIZATION OF ACYCLIC OLEFINIC ACIDS: THE *trans* AND *cis* ISOMERS OF 4,5-DIHYDRO-5-IODOMETHYL-4-PHENYL-2(3*H*)-FURANONE



Submitted by F. Bermejo Gonzalez and Paul A. Bartlett[1].
Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

A. *3-Phenyl-4-pentenoic acid*. A mixture of 33.7 g (0.25 mol) of cinnamyl alcohol (Note 1), 46.1 mL (0.25 mol) of triethyl orthoacetate (Note 1), and 0.19 mL (1.5 mmol) of hexanoic acid (Note 2) is placed in a 250-mL, round-bottomed flask equipped with a thermometer, Claisen head, and condenser. The solution is heated in an oil bath with distillation of ethanol. After 3 hr, distillation of ethanol slows and another 0.1-mL portion of hexanoic acid is added. Additional portions (0.1 mL) of the catalyst are added again at 3.5 and 4.5 hr. After 6 hr, a total of 27 mL of ethanol, out of a theoretical 29.2 mL, has been collected, and GC analysis (Note 3) indicates that no cinnamyl alcohol remains. Over this 6-hr period the internal temperature rises from 100 to 166°C.

The solution is allowed to cool, and 19.7 g (0.35 mol) of potassium hydroxide in 25 mL of water and 75 mL of methanol is added. The mixture is heated under reflux for 1 hr under nitrogen. After the alkaline solution is allowed to cool to room temperature, it is washed with ether and acidified with concentrated HCl. The acidic solution is extracted with three 50-mL portions of ether, and the organic layer is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield of crude 3-phenyl-4-pentenoic acid is 38–39 g (86–88%). This material is essentially pure by NMR analysis and can be used directly as starting material for the following iodolactonization reactions. The acid can be further purified by crystallization from hexane (86% recovery in two crops) to give product melting at 44–46°C.

B. *Thermodynamically controlled formation of the trans (4RS,5SR) isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone*. In a 500-mL, round-bottomed flask equipped with a mechanical stirrer (Note 4) and immersed in an ice bath is placed a solution of 10 g (0.057 mol) of 3-phenyl-4-pentenoic acid in 200 mL of acetonitrile (Note 5). Solid iodine (44.5 g, 0.18 mol) (Note 6) is added, and the mixture is protected from light and stirred at 0°C under nitrogen for 24 hr. The mixture is partitioned between 100 mL of ether and 100 mL of saturated aq $NaHCO_3$. The organic layer is washed with 10% aqueous $Na_2S_2O_3$ until colorless, and with water and brine. It is then dried over $MgSO_4$, the solvent is removed at reduced pressure, and the crude trans iodolactone is obtained as a thick oil; weight 14.5–15.6 g (85–91%). NMR analysis indicates that the trans : cis ratio is at least 95 : 5 (Note 7).

C. *Kinetically-controlled formation of the cis (4RS,5RS) isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone*. A mixture of 10 g (0.057 mol) of 3-phenyl-4-pentenoic acid, 9.1 g (0.11 mol) of $NaHCO_3$ and 200 mL of water is placed in a 1000-mL round-bottomed flask equipped with a mechanical stirrer (Note 4) and stirred until a homogeneous solution is obtained. Chloroform (200 mL) is added, the mixture is cooled in an ice bath, and 28.4 g (0.112 mol) (Note 8) of iodine is added. The mixture is stirred at 0°C for 6 hr, the layers are separated, and the organic phase is washed with 10% aqueous $Na_2S_2O_3$ until colorless, and with water and brine. The organic layer is dried over $MgSO_4$, the solvent is removed under reduced pressure, and the crude *cis*-iodolactone is obtained as a semisolid: weight 15.5–16.3 g (91–95%), mp 75–90°C (Note 9). Direct recrystallization of this material from diisopropyl ether (Note 10) affords 9.0–9.5 g (52–55%) of material, mp 103–104°C, with a cis : trans ratio of 15–16 : 1. Further recrystallization from diisopropyl ether gives (in two crops) 8.3–8.9 g (48–52%) of product, mp 104–105°C, with a purity of ≥98%. Additional product can be obtained from the mother liquors.

2. Notes

1. The reagents employed were obtained from Aldrich Chemical Company, Inc. and used as received.
2. Propionic acid may also be used as catalyst; however, its boiling point (141°C) is below that of the reaction temperature at the end of the reaction. The use of *o*-nitrophenol as catalyst resulted in a lower yield in this case.
3. Gas chromatographic analysis was performed on a Varian model 940 gas chromatograph equipped with a 6-in. × 1/8-in. column of 5% OV-101 on Gas-Chrom Q at a column temperature of 155°C.
4. A magnetic stirrer is not recommended because the mixture becomes very thick.
5. Mallinckrodt Inc. analytical reagent-grade acetonitrile was used.
6. Two equivalents of iodine are required by the stoichiometry of the reaction, because of formation of HI_3. In our experience, however, the reaction does not proceed to completion without additional reagent.
7. The crude trans isomer obtained in this way is of suitable purity for conversion to the epoxy ester, as described below (see Discussion). It may be further purified by column chromatography; however, attempted vacuum distillation leads to considerable decomposition.
8. Two equivalents of iodine are required because of formation of NaI_3.
9. NMR analysis of the crude iodolactone indicates that the cis : trans ratio is about 3.4:1.
10. The recrystallization is performed using ca. 15 mL of diisopropyl ether per gram of crude product. Dichloromethane, 1–2%, is also added to the hot mixture to effect complete solution before cooling.

3. Discussion

Iodolactonization has become a useful reaction for the stereocontrolled introduction of chiral centers in both cyclic[2] and acyclic[3,4,5,6,7,8,9] systems. Depending on the reaction conditions, the cyclization can be carried out under either kinetic or thermodynamic control.[3,10] The contrast between the stereochemical course of the two procedures is not always as dramatic as with 3-phenyl-4-pentenoic acid, as illustrated by the examples in Table I.[11] A procedure for obtaining high 1,3-asymmetric induction in formation of valerolactones by cyclization of *N,N*-dimethylamides has been reported,[12] and the tendency for an oxygen substituent in the allylic position to control the stereochemistry of electrophilic cyclization has been addressed.[13]

Conversion of iodolactones into the corresponding epoxy esters is often one of the major steps in their utilization for the purposes of stereocontrol.[3,4,5,6,7,14] Methanolysis of the cis isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3*H*)-furanone to methyl (3*RS*,4*RS*)-4,5-epoxy-3-phenylpentanoate is a representative procedure for this transformation.

A mixture of 5.0 g (16.6 mmol) of (4*RS*,5*RS*)-4,5-dihydro-5-iodomethyl-4-phenyl-2(3*H*)-furanone (cis isomer), 75 mL of methanol, and 1.8 g (17.0 mmol) of finely powdered, anhydrous Na_2CO_3 is placed in a 250-mL, round-bottomed flask equipped with a mechanical stirrer and heated under nitrogen at reflux for 8 hr. The resulting solution is concentrated under reduced pressure to a volume of 50 mL and partitioned between 100 mL of water and 100 mL of ether. The organic layer is washed with water and brine, dried over $MgSO_4$, and evaporated to give 3.1 g (91%) of crude product. This material, which shows only minor impurities by NMR spectroscopy, can be further purified by chromatography (silica

gel/1 : 1 ether : hexane) (98% recovery) and bulb-to-bulb distillation (78°C/0.045 mm) (82% recovery).

TABLE I
IODOLACTONIZATION OF OLEFINIC ACIDS

Substrate	Trans : Cis Ratio [Yield (%)] "Thermodynamic Control"	"Kinetic Control"
3-Methyl-4-pentenoic acid	10 : 1 (84)	1 : 3 (82)
4-Methyl-5-hexenoic acid	10 : 1 (77)	1 : 2.3 (83)
3-Methyl-5-hexenoic acid	1 : 6 (81)	1 : 3 (97)
2-Methyl-5-hexenoic acid	1.1 : 1 (68)	1.8 : 1 (78)
(2*RS*,4*SR*)-2,4-Dimethyl-5-hexenoic acid	20 : 1 (89)	3.5 : 1

References and Notes

1. Department of Chemistry, University of California, Berkeley, CA 94720.
2. Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev*. **1979**, *171*, and references cited therein.
3. Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc*. **1978**, *100*, 3950.
4. Chamberlin, A. R.; Dezube, M.; Dussault, P. *Tetrahedron Lett*. **1981**, *22*, 4611.
5. Bartlett, P. A.; Myerson, J. *J. Org. Chem*. **1979**, *44*, 1625.
6. Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc*. **1980**, *102*, 2118.
7. Mori, K.; Umemura, T. *Tetrahedron Lett*. **1982**, *23*, 3391.
8. Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc*. **1982**, *104*, 4708.
9. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.
10. Barnett, W. E.; Sohn, W. H. *J. Chem. Soc., Chem. Commun*. **1972**, 472; *Tetrahedron Lett*. **1972**, 1777.
11. Myerson, J., Ph.D. Dissertation, University of California, Berkeley, 1980.
12. Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.-I.; Yoshida, Z.-i.; Yanagi, K.; Kazunori, Y.; Minobe, M. *J. Am. Chem. Soc*. **1984**, *106*, 1079–1085.
13. Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc*. **1987**, *109*, 672–679.
14. House, H. O.; Carlson, R. G.; Muller, H.; Noltes, A. W.; Slater, C. D. *J. Am. Chem. Soc*. **1962**, *84*, 2614; Takano, S.; Hirama, M.; Ogasawara, K. *J. Org. Chem*. **1980**, *45*, 3729; Still, W. C.; Galynker, I. *J. Am. Chem. Soc*. **1982**, *104*, 1774.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

trans AND cis ISOMERS OF 4,5-DIHYDRO-5-IODOMETHYL-4-PHENYL-2(3H)-FURANONE

$Na_2S_2O_3$

trans iodolactone

cis-iodolactone

HI_3

NaI_3

valerolactones

N,N-dimethylamides

iodolactones

cis isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone

(4RS,5RS)-4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone (cis isomer)

(2RS,4SR)-2,4-Dimethyl-5-hexenoic acid

ethanol (64-17-5)

HCl (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

$NaHCO_3$ (144-55-8)

propionic acid (79-09-4)

Na_2CO_3 (497-19-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

hexanoic acid (142-62-1)

dichloromethane (75-09-2)

o-nitrophenol (88-75-5)

$MgSO_4$ (7487-88-9)

cinnamyl alcohol (104-54-1)

diisopropyl ether (108-20-3)

hexane (110-54-3)

triethyl orthoacetate (78-39-7)

3-Phenyl-4-pentenoic acid (5703-57-1)

4,5-Dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone

3-Methyl-4-pentenoic acid

4-Methyl-5-hexenoic acid

3-Methyl-5-hexenoic acid

2-Methyl-5-hexenoic acid

Methyl (3RS,4RS)-4,5-epoxy-3-phenylpentanoate (107445-25-0)