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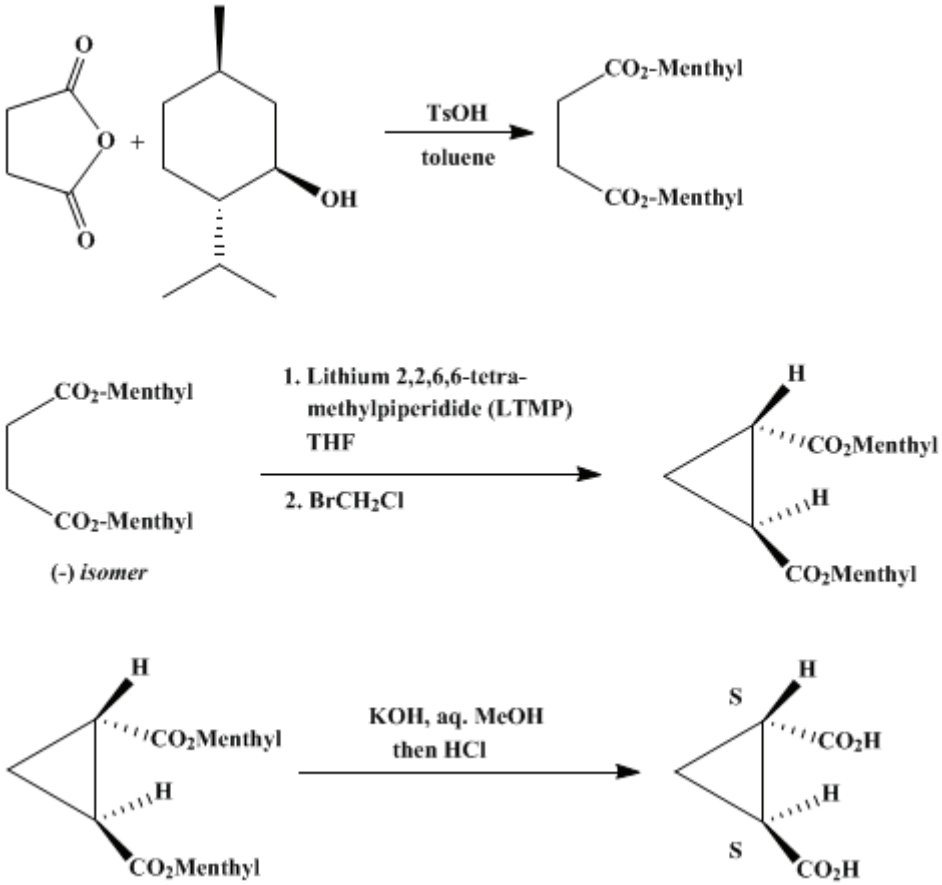
CONDENSATION OF (−)-DIMENTHYL SUCCINATE DIANION WITH 1,ω-DIHALIDES: (+)-(1*S*,2*S*)-CYCLOPROPANE-1,2-DICARBOXYLIC ACID

[1,2-Cyclopropanedicarboxylic acid, (1*S*,2*S*)-(+)-]



Submitted by Kyoji Furuta, Kiyoshi Iwanaga, and Hisashi Yamamoto[1].
Checked by Ichiro Mori and Clayton H. Heathcock.

1. Procedure

A. *(−)-Dimenthyl succinate.* A 300-mL. one-necked, round-bottomed flask is equipped with a magnetic stirrer, a Dean–Stark trap, and a reflux condenser. The flask is charged with 20 g (0.2 mol) of succinic anhydride, 62.5 g (0.4 mol) of *l*-menthol, 250 mg (1.3 mmol) of *p*-toluenesulfonic acid monohydrate, and 150 mL of toluene (Note 1). The mixture is heated under reflux in an oil bath (about 140°C) for 24 hr. During this period the theoretical amount of water (3.6 mL) is collected. The mixture is allowed to cool to ambient temperature, diluted with 200 mL of hexane, and poured into a mixture of 250 mL of aqueous saturated sodium bicarbonate, 100 mL of methanol, and 200 mL of water. The organic phase is separated and the aqueous phase is extracted twice with 100 mL of hexane. The organic phases are combined, washed once with 200 mL of saturated brine, and dried over sodium sulfate. The solvent is removed with a rotary evaporator, and the resulting crude product is dissolved in 100 mL of methanol. After the solution stands in a refrigerator overnight, colorless crystals appear in the mixture and are collected by filtration with suction (Note 2). This material (ca. 70 g in two crops) is purified by recrystallization from methanol to afford 66 g (84%) of pure (−)-dimenthyl succinate, mp 63–64°C (Note 3).

B. *(−)-Dimenthyl (1S,2S)-cyclopropane-1,2-dicarboxylate.* A dry, 500-mL, three-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a 100-mL pressure-equalizing dropping funnel, a rubber septum, and a three-way stopcock with a nitrogen inlet. The air in the system is replaced with dry nitrogen. The flask is charged with 180 mL of dry tetrahydrofuran and cooled with an ice bath; 74.1 mL of a 1.7 *M* hexane solution of butyllithium (126 mmol) (Note 4) is added. This solution is stirred while 21.3 mL (126 mmol) of 2,2,6,6-tetramethylpiperidine (Note 5) is added dropwise with a syringe through the septum over a 10-min period. The resulting solution of lithium 2,2,6,6-tetramethylpiperidide (LTMP) is cooled to −78°C with a dry ice–methanol bath (Note 6) and stirred. A solution of 23.7 g (60 mmol) of (−)-dimenthyl succinate in 50 mL of dry tetrahydrofuran is then added dropwise through the addition funnel over a 1-hr period. The wall of the funnel is rinsed with 10 mL of dry tetrahydrofuran and the rinse is added to the solution. The resulting yellow solution of succinate dianion is stirred for 1 hr. To the solution is added dropwise 3.9 mL (60 mmol) of bromochloromethane (Note 7) with a syringe through the septum over a 10-min period. After the reaction mixture is stirred for 2 hr (Note 8), 2.2 mL (24 mmol) of isobutyraldehyde (Note 9) is added dropwise to quench any unreacted anions (Note 10). After being stirred for an additional 30 min, the reaction mixture is poured into 250 mL of ice-cooled 1 *N* hydrochloric acid and the product is extracted 3 times with 150 mL of ether. The combined organic phases are washed with 250 mL of brine, dried over sodium sulfate, filtered, and concentrated with a rotary evaporator. The residue is chromatographed on 700 g of silica gel (Note 11) packed in a 9.5-cm-diameter column using a mixture of ether and hexane (1 : 18) as eluant. The appropriate fractions are collected and concentrated to give 11.5 g (47%) of (−)-dimenthyl (1*S*,2*S*)-cyclopropane-1,2-dicarboxylate as colorless crystals. Analysis by GC indicates a diastereomeric ratio of 96 : 4 (Note 12). Recrystallization of this material from 25 mL of methanol affords 9–10 g (38–40%) (Note 13) of optically pure product, mp 95–96°C (Note 14).

C. *(+)-(1S,2S)-Cyclopropane-1,2-dicarboxylic acid.* (−)-Dimenthyl (1*S*,2*S*)-cyclopropane-1,2-dicarboxylate (4.06 g, 10 mmol, $[\alpha]_D^{25}$ + 17.8°) is dissolved in 20 mL of a 10% potassium hydroxide solution in 9 : 1 methanol/water in a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar. The solution is heated at 60°C with an oil bath. Progress of the reaction is monitored by TLC on silica gel, using 1 : 1 hexane/ethyl acetate as eluant (Note 15). After about 4 hr the resulting two-phase mixture is diluted with 20 mL of water and extracted with three 40-mL portions of ether (Note 16). The aqueous layer is acidified by the addition of 20 mL of ice-cold 6 *N* hydrochloric acid, saturated with ca. 5 g of sodium chloride, and extracted with five 40-mL portions of ether. The combined organic layers are dried over sodium sulfate, diluted with 5 mL of hexane, and concentrated with a rotary evaporator. Filtration provides 1.17 g (90%) of (+)-(1*S*,2*S*)-cyclopropane-1,2-dicarboxylic acid, mp 172–173°C, $[\alpha]_D^{25}$ +228° (ethanol, *c* 1.01) [lit.[2] mp 169.5–170°C, $[\alpha]_D^{25}$ +227.9° (ethanol, *c* 2.342)] (Note 17).

2. Notes

1. Succinic anhydride and *p*-toluenesulfonic acid monohydrate were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Guaranteed-grade *l*-(−)-menthol was purchased from Tokyo Kasei Kogyo Company, Ltd. (Japan). Reagent-grade toluene was dried and stored over sodium metal. The checkers obtained *p*-toluenesulfonic acid from Eastman Kodak and succinic anhydride and *l*-(−)-menthol from the Aldrich Chemical Company, Inc.
2. In the first trial the checkers experiences difficulty in crystallization at this point, even after keeping the solution in a 5°C refrigerator for 4 days. Crystallization was induced by cooling the crude product (ca. 80 g of oil) to −78°C in a methanol–dry ice bath. Ether (5 mL) was added to the resulting glass, the cooling bath was removed, and the surface of the solid material was scratched continuously with a spatula. At about 0°C the glass began to melt and small white spots appeared. Continued stirring of the viscous material as it warmed resulted in crystallization of the entire mass. The crystalline mass was dried under vacuum and a small portion kept as seed crystals. The remainder was dissolved in 100 mL of warm methanol. After the solution was cooled to room temperature, a small quantity of the seed material was added and the solution was placed in a 5°C refrigerator overnight. Approximately 68 g of crystalline (−)-dimenthyl succinate was obtained. The filtrate was condensed with a rotary evaporator and cooled again to give another 2.6 g. In subsequent trials, the foregoing procedure was not necessary as the crude diester crystallized spontaneously, giving a similar yield in two crops.
3. The submitters report mp 65–66°C. The physical properties are as follows: ^{1}H NMR ($CDCl_3$, 250

MHz) δ: 0.70–2.02 (complex, 18 H), 0.75 (d, 6 H, J = 6.9), 0.89 (d, 12 H, J = 6.4), 2.60 (s, 4 H), 4.70 (dt, 2 H, J = 4.4, 10.8); $[\alpha]_D^{25}$ −88.7° ($CHCl_3$, c 1.02).

4. Tetrahydrofuran was freshly distilled from sodium–benzophenone. Butyllithium was obtained from Wako Pure Chemical Industries, Ltd. or Foote Mineral Company. It was titrated with anhydrous 2-butanol using 1,10-phenanthroline as an indicator.

5. 2,2,6,6-Tetramethylpiperidine, purchased from Tokyo Kasei Kogyo Company, Ltd. or Aldrich Chemical Company, Inc., was used. The use of this sterically hindered lithium amide is crucial for high diastereoselectivity. If lithium diisopropylamide is used, the diastereoselectivity of the reaction is reduced significantly.[3]

6. The flask was cooled with a dry ice–methanol bath for 30 min before subsequent addition.

7. Bromochloromethane was purchased from Tokyo Kasei Kogyo Company, Ltd. or from Aldrich Chemical Company, Inc. and was used without purification.

8. TLC (ether–hexane) showed residual starting material.

9. Isobutyraldehyde was obtained from Wako Pure Chemical Industries, Ltd. or from Aldrich Chemical Company, Inc. and was used without purification.

10. This procedure was not essential but facilitated the subsequent chromatographic separation of desirable product from residue.

11. Silica gel (70–200 mesh) purchased from Fuji Davison Chemical (BW-820 MH) was used. The checkers used silica gel (230–400 mesh) purchased from Merck (Kieselgel 60).

12. GC analysis was performed with a capillary column (PEG, 0.25 mm × 25 m) purchased from Gaskuro Kogyo Company, Ltd. (Japan). The checkers used a 0.2-mm × 25-m Carbowax 20 M capillary column. The diastereomeric excess ranged from about 80–92%. In all cases, however, essentially pure material could be obtained by a subsequent single recrystallization. The diastereomeric ratio can be further improved by reducing the amount of added bromochloromethane. This may be due to the stereochemical purity of the enolates. On treatment with lithium 2,2,6,6-tetramethylpiperidide, the succinate affords mainly the *E,E*-enolate and only a slight amount of *Z,Z*-enolate; the latter may induce the opposite stereochemistry in the product. Fortunately, the *E,E*-enolate is more reactive, and therefore, the undesirable reaction with *Z,Z*-enolate can be suppressed, kinetically by reducing the amount of halide. Thus the use of 0.5 equivalent of bromochloromethane compared to starting ester results in over 99% diastereoselectivity with comparable chemical yield, based on the halide. The procedure described in the text is, however, recommended from a practical point of view.

13. This yield ranges from 38 to 57% in several experiments. Recrystallization was accomplished by dissolving the crude diester in warm methanol and then allowing this solution to cool to room temperature. The checkers found that, if crystallization was induced by cooling the methanol solution in a refrigerator, the crystalline diester was accompanied by an oily by-product. A second recrystallization was then necessary to purify the material.

14. The submitters report mp 99–100°C. The physical properties are as follows: ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.70–2.02 (complex, 20 H), 0.76 (d, 6 H, J = 7.0), 0.90 (d, 12 H, J = 6.8), 2.12. (dd, 2 H, J = 7.4, 7.2), 4.68 (dt, 2 H, J = 5.4, 10.9); $[\alpha]_D^{25.5}$ + 17.8° ($CHCl_3$, c 1.0).

15. During the course of the saponification, a spot with R_f intermediate between that of the reactant and product (presumably the monoester) was observed.

16. The combined organic layer may be washed with 50 mL of brine, dried over sodium sulfate, and evaporated to recover 3.45 g of crude menthol.

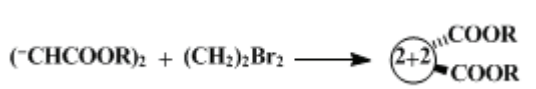
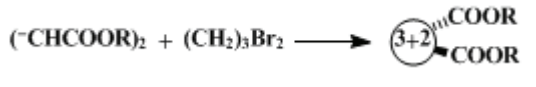
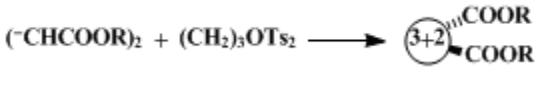
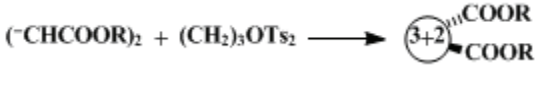
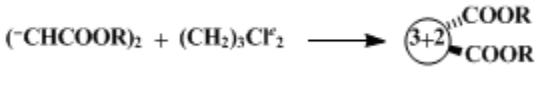
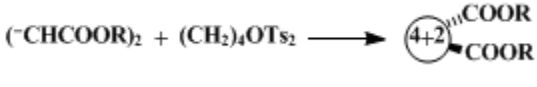
17. The checkers note that in the paper by Inouye et al.[2] the diacid was prepared by ozonolysis of (+)-*trans*-2-phenylcyclopropanecarboxylic acid having 96.3% optical purity. The product diacid was purified by sublimation and recrystallization from water to obtain material giving the cited physical properties. Although the original publication[2] claims an optical purity of 96.3% for this diacid, it is probably optically pure because of the recrystallization step.

3. Discussion

The procedure described here provides a simple and general method for the construction of optically active *trans*-cycloalkane-1,2-dicarboxylic acids.[3] The reaction has been applied successfully to a series of dihalides and ditosylates (Table I).

TABLE I

ASYMMETRIC SYNTHESIS OF CYCLOALKANE DICARBOXYLATES

Electrophile X	*n*	Yield (%)	Diastereomeric Excess (%)	Configuration
 Br	2	72	—[a,b]	—[c]
 Br	3	77	65	*S,S*
 OTs	3	63	92	*S,S*
 OTs	3	64	88	*R,R*[d]
 Cl[e]	3	57	83[a]	—[c]
 OTs	4	61	75	*S,S*

[a]Reaction first at −100°C, and then warming to −20°C.
[d]Not determined. $[\alpha]_D^{25}$ −51.7° ($CHCl_3$, *c* 1.0).
[c]Not determined.
[d]*d*-Menthyl ester was used.
[e]3-Chloro-2-chloromethyl-1-propene.

A few methods are described in the literature for the preparation of optically active dialkyl *trans*-cyclopropane-1,2-dicarboxylates,[2] including a Michael addition–condensation sequence of menthyl chloroacetate and menthyl acrylate,[4] and cobalt(0) or nickel(0) complex-catalyzed cyclopropanation of dimenthyl fumarate with dibromomethane.[5] The present method is characterized by good chemical and high optical yields, simple operation, preparation of both enantiomers with equal ease, and the ready availability of the starting materials.

References and Notes

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

Lithium 2,2,6,6-tetramethylpiperidide

brine

(−)-Dimenthyl succinate

(−)-Dimenthyl (1S,2S)-cyclopropane-1,2-dicarboxylate

lithium 2,2,6,6-tetramethylpiperidide (LTMP)

l-(−)-menthol

trans-cycloalkane-1,2-dicarboxylic acids

d-Menthyl ester

trans-cyclopropane-1,2-dicarboxylates

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

nickel(0) (7440-02-0)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

menthol,
l-menthol (15356-60-2)

dibromomethane (74-95-3)

Succinic anhydride (108-30-5)

isobutyraldehyde (78-84-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

SUCCINATE DIANION

lithium amide (7782-89-0)

hexane (110-54-3)

cobalt(0) (7440-48-4)

2-Butanol (78-92-2)

p-toluenesulfonic acid (104-15-4)

lithium diisopropylamide (4111-54-0)

1,10-phenanthroline (66-71-7)

2,2,6,6-tetramethylpiperidine (768-66-1)

bromochloromethane (74-97-5)

(+)-(1S,2S)-Cyclopropane-1,2-dicarboxylic acid,
1,2-Cyclopropanedicarboxylic acid, (1S,2S)-(+)- (14590-54-6)

3-Chloro-2-chloromethyl-1-propene (1871-57-4)

menthyl chloroacetate

menthyl acrylate

dimenthyl fumarate

p-toluenesulfonic acid monohydrate (6192-52-5)

(+)-trans-2-phenylcyclopropanecarboxylic acid (939-90-2)