

## ASYMMETRIC REACTIONS. XLIII.\*

## ASYMMETRIC SIMMON-SMITH REACTION

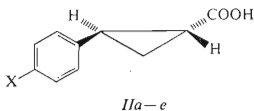
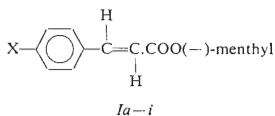
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Asymmetric addition of methylene generated from diiodomethane and Zn/Cu alloy to (-)-menthyl esters of substituted *trans*-cinnamic acids (*Ia-i*) gives rise, after hydrolysis, to partially optically active substituted *trans*-(-)-2-phenylcyclopropanecarboxylic acids (*Ila-e*) to which the absolute configuration 1*R*,2*R* has been assigned.

Literature describes several cases of asymmetric synthesis of cyclopropane derivatives during which an auxiliary chirality center is present either in the added component<sup>1</sup> or in the unsaturated compound<sup>2-4</sup>. In this study we added methylene, generated from diiodomethane and an alloy of zinc and copper under the conditions of Simmon-Smith reaction, to (-)-menthyl esters of substituted *trans*-cinnamic acids (*Ia-i*).



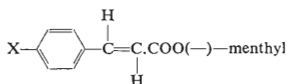
X = a H; b CH<sub>3</sub>; c OCH<sub>3</sub>; d Br; e Cl; f F; g (CH<sub>3</sub>)<sub>2</sub>N; h *p*-NO<sub>2</sub>; i *m*-NO<sub>2</sub>.

By introducing ozone we eliminated the unreacted substituted (-)-menthyl cinnamate and applying subsequently alkaline hydrolysis we obtained levorotatory substituted *trans*-2-phenylcyclopropanecarboxylic acids (*IIa-e*) which we purified by sublimation and crystallisation<sup>5</sup>. The cyclopropane ring was formed easily in the case of esters *Ia-e*. In contrast to this we were unable to isolate cyclopropane derivatives in the case of esters *If-i*, probably because either the nitro group did not react with activated zinc, or changes took place during the isolation, as for example in the case of ester *Ig*. The unreactivity of ester *If* remains unexplained. The results are listed in Table I and II.

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As of the compounds obtained only the acid *Ila* is known in optically pure form<sup>6</sup>, we tried to reduce off the halogen in compounds *Ild,e* in order to compare optical yields from absolute configuration. We found that on catalytic hydrogenation of compounds *Ild,e* and the unsubstituted acid *Ila* on palladium in ethanol the reductive elimination of halogen took place under simultaneous hydrogenolytic cleavage of the ring<sup>7</sup>. From the reaction mixture we isolated in all instances in addition to hydrocinnamic acid also (*R*)-(+)- $\alpha$ -methyl- $\beta$ -phenylpropionic (*III*) and (*R*)-(–)- $\beta$ -methyl- $\beta$ -phenylpropionic acids (*IV*) the absolute configurations of which are known. The cyclopropane ring was not cleaved on reduction of acids *Ila,d,e* with

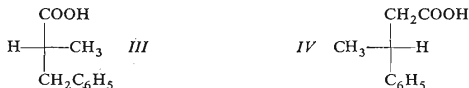
TABLE I

(–)-Menthyl Esters of Substituted Cinnamic Acids *Ia–i*

Ester	M.p., °C (ethanol)	[ $\alpha$ ] <sub>D</sub> <sup>20</sup> (c 10, chloroform)	Formula (m.w.)	Calculated/Found		
				% C	% H	% X
<i>Ia</i>	38	–62.3	C <sub>19</sub> H <sub>26</sub> O <sub>2</sub> (286.4)	79.68 79.41	9.15 9.14	—
<i>Ib</i>	50–51	–55.0	C <sub>20</sub> H <sub>28</sub> O <sub>2</sub> (300.4)	79.95 79.69	9.39 9.18	—
<i>Ic</i>	54–55	–50.6	C <sub>20</sub> H <sub>28</sub> O <sub>3</sub> (316.4)	79.51 79.45	8.99 9.03	—
<i>Id</i>	64–65	–45.6	C <sub>19</sub> H <sub>25</sub> BrO <sub>2</sub> (366.4)	62.53 62.77	6.85 6.91	21.87 Br 22.42 Br
<i>Ie</i>	72–73	–52.4	C <sub>19</sub> H <sub>25</sub> ClO <sub>2</sub> (320.9)	71.22 71.26	7.85 7.98	11.05 Cl 11.27 Cl
<i>If</i>	57–58	–55.2	C <sub>19</sub> H <sub>25</sub> FO <sub>2</sub> (304.4)	74.99 75.00	8.28 8.39	6.24 F 6.60 F
<i>Ig<sup>a</sup></i>	98	63.9	C <sub>21</sub> H <sub>31</sub> NO <sub>2</sub> (311.4)	76.66 76.39	9.50 9.56	4.25 N 4.38 N
<i>Ih</i>	92–93	–67.3	C <sub>19</sub> H <sub>25</sub> NO <sub>4</sub> (331.4)	68.86 68.70	7.60 7.51	4.22 N 3.98 N
<i>Ii</i>	85	–70.6	C <sub>19</sub> H <sub>25</sub> NO <sub>4</sub> (331.4)	68.86 68.88	7.60 7.90	4.22 N 4.24 N

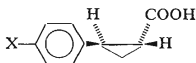
<sup>a</sup> Prepared from (–)-menthyl acetate and *p*-dimethylaminobenzaldehyde<sup>10</sup>.

sodium bis(2-methoxyethoxy)dihydridoaluminumate, but gave rise, under simultaneous reductive splitting off of halogen, in all cases to *trans*-(-)-2-phenyl-1-hydroxymethylcyclopropane. The optical yield was approximately equal in these cases, *i.e.* about 12%.



Walborsky and coworkers<sup>6</sup> assigned to *trans*-(+)-2-phenylcyclopropanecarboxylic acid the absolute configuration 1*S*, 2*S* by transforming it to *trans*-cyclopropane-1,2-dicarboxylic acid of known absolute configuration. This was later also confirmed by Japanese authors<sup>8</sup>. In agreement with these results is the isolation of (*R*)-(+)- $\alpha$ -methyl- $\beta$ -phenylpropionic acid (*III*) and (*R*)-(-)- $\beta$ -methyl- $\beta$ -phenylpropionic acid (*IV*) from the hydrogenolytic cleavage of acids *Ila, d, e*, and similarly of (1*R*,2*R*)-*trans*-(-)-2-phenyl-1-hydroxymethylcyclopropane from their reduction with sodium bis(2-methoxyethoxy)dihydridoaluminumate. The absolute configuration of acids *Ila–e* further follows from the comparison of their ORD curves. The ORD curves measured in etha-

TABLE II

Substituted *trans*-(-)-2-Phenylcyclopropanecarboxylic Acids (*Ila–e*)

Acid (m.p., °C)	Total yield (optical yield) %	[ $\alpha$ ] <sub>D</sub> <sup>20a</sup>	Formula (m.w.)	Calculated/Found		
				% C	% H	% X
<i>Ila</i> 84–86 <sup>b</sup>	56 (11·0)	-34·0	C <sub>10</sub> H <sub>10</sub> O <sub>2</sub> (162·2)	74·05 73·89	6·22 6·29	—
<i>Ilb</i> 106–107 <sup>c</sup>	42 (10·5)	-22·8	C <sub>11</sub> H <sub>12</sub> O <sub>2</sub> (176·2)	74·98 74·71	6·87 6·52	—
<i>Ilc</i> 100–101 <sup>d</sup>	26 (8·8)	-15·0	C <sub>11</sub> H <sub>12</sub> O <sub>3</sub> (192·3)	68·73 68·60	6·29 6·46	—
<i>Ild</i> 112–113 <sup>e</sup>	33 (11·4)	-22·1	C <sub>10</sub> H <sub>9</sub> BrO <sub>2</sub> (242·1)	49·50 49·60	3·76 3·44	32·98 Br 32·10 Br
<i>Ile</i> 109–110 <sup>f</sup>	52 (9·8)	-31·8	C <sub>10</sub> H <sub>9</sub> ClO <sub>2</sub> (196·7)	61·15 61·04	4·68 4·98	18·04 Cl 18·06 Cl

<sup>a</sup> In methanol, *c* 2; <sup>b</sup> racemic compounds 91–91·5°C (ref.<sup>11</sup>); <sup>c</sup> 119·5–120·5°C (ref.<sup>12</sup>); <sup>d</sup> 112–113°C (ref.<sup>12</sup>); <sup>e</sup> 126–127°C (ref.<sup>13</sup>); <sup>f</sup> 116–117°C (ref.<sup>11</sup>).

nol display two negative Cotton effects, in agreement with their UV spectra; the first is about 270 nm, corresponding to the  ${}^1L_b$  band of the aromatic nucleus, and the second — under 250 nm — is formed probably by the superimposition of the  ${}^1L_a$  band with the  $n-\pi^*$  transition of the carbonyl group<sup>9</sup>. The levorotatory acids *IIa-e* have the absolute configuration 1*R*,2*R*.

## EXPERIMENTAL

The melting and boiling points given are uncorrected. Analytical samples were dried *in vacuo* (oil pump) at room temperature for 8 h. The optical rotations were measured on a polarimeter with a 0.02° accuracy, the ORD curves on a Jasco UV 5 apparatus.

### (-)-Menthyl Esters of Substituted Cinnamic Acids *Ia-i*

The substituted cinnamic acid (0.5 mol) obtained on condensation of the corresponding substituted benzaldehyde with malonic acid in pyridine under catalysis of a small amount of piperidine, was refluxed with 185 ml of thionyl chloride for 2 h. After evaporation of the reaction mixture to dryness 165 g (1 mol) of (-)-menthol was added to the residue and the mixture heated at 130°C for 3 hours. The excess menthol was distilled off *in vacuo*. The product was first distilled and then crystallised (Table I).

### Substituted *trans*-(-)-2-Phenylcyclopropanecarboxylic Acids (*IIa-e*)

The Zn-Cu alloy prepared from cupric acetate and zinc powder was refluxed with 27 g of diiodomethane and 0.05 mol of ester *Ia-e* in 150 ml of ether for 3 days. The mixture was decomposed by pouring it into a saturated ammonium chloride solution and the ethereal layer was washed first with 5% sodium thiosulphate solution, then with water, and dried over anhydrous magnesium sulfate. After evaporation of ether the residue was dissolved in 250 ml of tetrachloromethane and oxygen enriched with ozone was introduced into it. When the consumption of ozone ceased the violet solution was shaken with 250 ml of a 10% KOH and 30 ml of 30% H<sub>2</sub>O<sub>2</sub> solution for 3 h. After standing overnight the organic layer was separated, evaporated, and the residue hydrolysed by 12 h boiling with 150 ml of 10% KOH in a mixture of ethylene glycol and water (2 : 1). After dilution with water (-)-menthol was eliminated by extraction with ether and the acid was precipitated by acidification. It was extracted with ether, the solvent evaporated and the residue purified by distillation and crystallisation (Table II).

### Catalytic Hydrogenation of Substituted (-)-*trans*-2-Phenylcyclopropanecarboxylic Acids (*IIa,d,e*)

Acids *IIa,d,e* were hydrogenated on palladium on charcoal in ethanol. When the consumption of hydrogen attained the supposed value the formed mixture of acids was extracted with 5% NaOH. The acids precipitated on acidification were extracted with ether and isolated by distillation. The mixture of acids obtained on hydrogenation of compound *IIa* boiled at 156–162°C/10 Torr,  $[\alpha]_D^{20} -1.3^\circ$  (c 2, methanol), that obtained from *IId* had b.p. 158–162°C/12 Torr,  $[\alpha]_D^{20} -2.9^\circ$  (c 4, methanol), and that from *IIe* had b.p. 152–155°C/9 Torr,  $[\alpha]_D^{20} -2.6^\circ$  (c 2, methanol). Chromatography on 20% Carbowax 20M on Celite (200°C) gave in the first case in addition to hydrocinnamic acid also acid *III*,  $[\alpha]_D^{20} +2.55^\circ$  (substance), and acid *IV*,  $[\alpha]_D^{20} -5.91^\circ$  (substance). For optically pure substances literature gives in the case of acid *III*<sup>14</sup>  $[\alpha]_D^{20} +20.4^\circ$

(substance), and of acid  $IV^{15}$   $[\alpha]_D^{20} -56.5^\circ$  (substance). In other cases the composition of the mixtures differed only negligibly.

Reduction of Substituted (-)-*trans*-2-Phenylcyclopropanecarboxylic Acids *Ila,d,e* with Sodium Bis(2-methoxyethoxy)dihydridoaluminate

A 68.6% solution of sodium bis(2-methoxyethoxy)dihydridoaluminate in benzene (2.7 ml) was evaporated and benzene was substituted by 1.5 ml of toluene. The solution was mixed with 1.3 mmol of acid *Ila,d,e* and the reaction mixture refluxed under nitrogen for 2 h. After cooling the reaction mixture was decomposed with 5 ml of 5% HCl and the insoluble part was extracted with 5 ml of benzene. After evaporation of benzene (-)-*trans*-2-phenyl-1-hydroxymethylcyclopropane was isolated from acid *Ila*; yield 82%, b.p. 93–95°C/3 Torr,  $[\alpha]_D^{20} -9.6^\circ$  (c 1.2, methanol). For  $C_{10}H_{12}O$  (148.2) calculated: 81.04% C, 8.16% H; found: 80.90% C, 8.26% H. From acid *Ild* the yield was 62%, b.p. 94.96°C/3 Torr,  $[\alpha]_D^{20} -12.2^\circ$  (c 0.8, methanol); found: 80.76% C, 8.20% H. From acid *Ile*, yield 54%, m.p. 93–96°C/4 Torr,  $[\alpha]_D^{20} -8.12^\circ$  (c 0.7, methanol); found: 80.44% C, 8.38% H.

REFERENCES

1. Tömösközi I.: *Tetrahedron* **19**, 1969 (1963).
2. Savada S., Takenana K., Inouye Y.: *J. Org. Chem.* **33**, 1767 (1968).
3. Nozaki H., Ito H., Tunemoto D., Kondo K.: *Tetrahedron* **22**, 441 (1966).
4. Nozaki H., Kondo K., Nakanisi Y., Sisido K.: *Tetrahedron* **19**, 1617 (1963).
5. Červinka O., Kříž O.: *Z. Chem.* **11**, 63 (1971).
6. Inouye Y., Sugita T., Walborsky H. M.: *Tetrahedron* **20**, 1695 (1964).
7. Parham W. E., Braxton H. C. jr, Serves C. jr: *J. Org. Chem.* **26**, 1831 (1961).
8. Aratani T., Nakanisi Y., Nozaki H.: *Tetrahedron* **26**, 1675 (1970).
9. Verbit L., Inouye Y.: *J. Am. Chem. Soc.* **89**, 5717 (1967).
10. McCluskey K. L., Sher B. C.: *J. Am. Chem. Soc.* **49**, 452 (1927).
11. Tchugaeff L.: *Ber.* **31**, 360 (1898).
12. Trachtenberg E. N., Odian G.: *J. Am. Chem. Soc.* **80**, 4015 (1958).
13. Fuchs R., Kaplan C. A., Bloomfield J. J., Hatch L. F.: *J. Org. Chem.* **27**, 733 (1962).
14. Prelog V., Scherrer H.: *Helv. Chim. Acta* **42**, 2227 (1959).
15. Cram D. J.: *J. Am. Chem. Soc.* **74**, 2137 (1952).

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