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PARTIAL ASYMMETRIC SYNTHESIS OF 2-ARYLCYCLOPROPANE CARBOXYLIC ACIDS BY THE REACTION OF SULPHUR YLIDES WITH β-ARYLACRYLATES[1]

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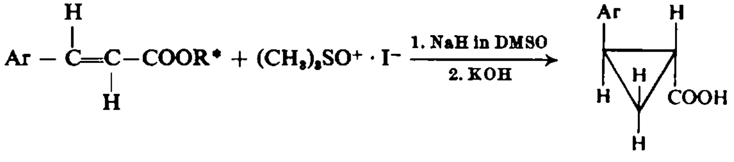
Abstract—Condensation of (−)-menthyl or (+)-bornyl β-arylacrylates (I) and dimethyloxosulphonium methylide or dimethylsulphonium methylide followed by alkaline hydrolysis gave optically active 2-arylcyclopropane carboxylic acids. Chemical yields of the cyclopropane derivatives decreased successively in the following order in the reaction of the cinnamates with: (a) trimethyloxosulphonium iodide in the presence of sodium hydride or potassium t-butoxide in dimethylsulphoxide solution, (b) trimethyloxosulphonium chloride, sodium hydride in tetrahydrofuran solution and (c) trimethylsulphonium iodide, sodium hydride in dimethylsulphoxide solution. Irrespective of the nature of the asymmetry-inducing centres and the method of condensation, cinnamates with or without ring-substituents gave, after hydrolysis, predominantly *laevorotatory* 2-arylcyclopropane carboxylic acids, while β-(α-naphthyl)acrylates afforded the *dextrorotatory* compounds in excess.

Partial asymmetric synthesis of *trans*-2-phenylcyclopropane carboxylic acid (IIIa) has been the subject of recent investigations.[2] The increasing amount of information on the synthesis of cyclopropane derivatives utilizing sulphur ylides[3] has prompted reinvestigation of the title problem by means of the reaction of dimethyloxosulphonium methylide[4] or dimethylsulphonium methylide[5] with β-arylacrylates (I).[6] Properties, yields and analyses of the acrylates (I) used are given in Table 1.



I II III

Ia, IIIa: Ar = C_6H_5—
Ib, IIIb: Ar = p-CH_3O—C_6H_4—
Ic, IIIc: Ar = o-CH_3O—C_6H_4—
Id, IIId: Ar = α-Naphthyl-

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[1] Partly presented at the 18th Annual Meetings of the Chemical Society of Japan, Osaka, April 2, 1965.

[2a] H. Nozaki, K. Kondô, O. Nakanisi and K. Sisido, *Tetrahedron* **19**, 1617 (1963); [b] I. Tömösközi, *Angew. Chem.* **75**, 294 (1963); *Tetrahedron* **19**, 1969 (1963); [c] D. B. Denney, J. J. Vill and M. J. Boskin, *J. Amer. Chem. Soc.* **84**, 3944 (1962).

[3] For the reaction of sulphur ylides with olefins affording cyclopropane derivatives, [a] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.* **84**, 3782 (1962); [b] E. J. Corey and M. Chaykovsky, *Tetrahedron Letters* 169 (1963); [c] P. T. Izzo, *J. Org. Chem.* **28**, 1713 (1963); [d] V. Franzen and H. E. Driesen, *Chem. Ber.* **96**, 1881 (1963); [e] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.* **87**, 1345 (1965); [f] V. J. Hruby and A. W. Johnson, *Ibid.* **84**, 3586 (1962), A. W. Johnson, V. J. Hruby and J. L. Williams, *Ibid.* **86**, 918 (1964).

[4] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.* **84**, 867 (1962).

[5] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.* **84**, 3782 (1962).

[6] (−)-Menthyl and (+)-bornyl cinnamates (Ia) are known, see K. L. McCluskey and B. C. Sher, *J. Amer. Chem. Soc.* **49**, 452 (1927); T. P. Hilditch, *J. Chem. Soc.* **93**, 7 (1908).

The reaction of trimethyloxosulphonium iodide (II) with (−)-menthyl or (+)-bornyl β-arylacrylates (I) in dimethylsulphoxide, followed by hydrolysis, yields optically active 2-arylcyclopropane carboxylic acids (III). The results summarized in Table 2 show, that, irrespective of the kind of asymmetry-inducing groups present in the cinnamates, the *trans*-2-phenyl- and 2-(*o*- or *p*-methoxyphenyl)-cyclopropane carboxylic acids (IIIa, IIIb and IIIc) produced are all *laevorotatory*, whereas 2-(α-naphthyl)-cyclopropane carboxylic acid (IIId) is obtained in *dextrorotatory* form.

TABLE 1. OPTICALLY ACTIVE β-ARYLACRYLATES: AR—CH═CH—COOR* (I)

Ar	R*[a]	B.p. (°C/mm)	M.p. (°C)	$[\alpha]_D$[b]	Yield[c] (%)
Ph[d]	−M	193–195/1·5		−59·7	76
Ph	+B	157–161/0·5		+36·7[e]	65
p-$CH_3OC_6H_4$	−M[f]	180–185/1·0		−48·1	50
p-$CH_3OC_6H_4$	+B[g]	181–182/1·0	52–55	+28·3	50
o-$CH_3OC_6H_4$	−M[h]	190–193/1·0		−48·2	34
o-$CH_3OC_6H_4$	+B[i]	192–196/1·5	81–84	+34·1	35
α-Naphthyl	−M[j]		67–70	−55·2[k]	21
α-Naphthyl	+B[l]		82–85	+29·1[k]	55

[a] −M for (−)-menthyl and +B for (+)-bornyl.

[b] Unless otherwise mentioned, optical rotations were measured in chloroform.

[c] Based on the corresponding acyl chloride.

[d] See Ref. 6.

[e] Measured in MeOH.

[f] Found: C, 75·58; H, 8·68. $C_{20}H_{28}O_3$ requires: C, 75·91; H, 8·92%.

[g] Found: C, 76·02; H, 8·17. $C_{20}H_{26}O_3$ requires: C, 76·40; H, 8·34%.

[h] Found: C, 75·94; H, 8·97. $C_{20}H_{28}O_3$ requires: C, 75·91; H, 8·92%.

[i] Found: C, 76·41; H, 8·39. $C_{20}H_{26}O_3$ requires: C, 76·40; H, 8·34%.

[j] Found: C, 82·50; H, 8·76. $C_{23}H_{28}O_2$ requires: C, 82·10; H, 8·39%.

[k] Measured in benzene.

[l] Found: C, 82·38; H, 8·12. $C_{23}H_{26}O_2$ requires: C, 82·59; H, 7·84%.

Further, (−)-menthyl cinnamates give higher optical yields than the (+)-bornyl compounds in the reaction of Ia, Ib and Ic. In the formation of 2-(α-naphthyl)-cyclopropane carboxylic acid (IIId), however, the (+)-bornyl group appears to be an even more effective inducing centre than the (−)-menthyl group. Finally, the optical yields of IIIa obtained in the (−)-menthyl reaction are 3–4% the calculation being based on the known magnitude of rotation.[7] These statements have been confirmed by duplication of the experiments. No definite conclusion could be drawn regarding the effects of ring-substituents on the chemical and optical yields of cyclopropane carboxylic acids (III).[8]

Asymmetric synthesis of 2-phenylcyclopropane carboxylic acid (IIIa) under varying conditions of condensation are shown in Table 3. The use of potassium t-butoxide as a base[9] instead of sodium hydride in dimethylsulphoxide gives somewhat higher chemical yields without affecting the optical yields.

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[7] Y. Inouye, T. Sugita and H. M. Walborsky, *Tetrahedron* **20**, 1695 (1964).

[8] Attempted asymmetric synthesis of cyclopropane carboxylic acid (III) utilizing the Simmons-Smith reaction of cinnamates I, H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.* **81**, 4265 (1959), failed even with methoxy substituted cinnamates (Ib, Ic).

[9] A dramatic difference was demonstrated recently in the behaviour of dihalides with sodium methylsulphinyl carbanion and potassium t-butoxide in dimethylsulphoxide; C. G. Cardenas, A. N. Khafaji, C. L. Osborn and P. D. Gardner, *Chem. and Ind.* 345 (1965).

TABLE 2. 2-ARYLCYCLOPROPANECARBOXYLIC ACIDS (III) FROM THE ACRYLATES I AND TRIMETHYLOXOSULPHONIUM IODIDE (II) IN THE PRESENCE OF SODIUM HYDRIDE IN DIMETHYLSULPHOXIDE[a]

Acrylate (I)		2-Arylcyclopropanecarboxylic acid (III)[b]			
Ar	R*	Yield (%)	α_D[c]	c	$[\alpha]_D$
Ph	−M	42	−0·359	3·73	−9·6
		49	−0·370	3·48	−10·6
Ph	+B	41	−0·047	2·31	−2·0
		35	−0·062	2·13	−2·9
p-$CH_3OC_6H_4$	−M	57	−0·085	2·57	−3·4
		41	−0·120	2·76	−4·3
p-$CH_3OC_6H_4$	+B	63	−0·025	1·96	−1·3
		13	−0·043	1·93	−2·2
o-$CH_3OC_6H_4$	−M	20	−0·080	1·05	−7·6
		18	−0·160	1·17	−13·7
o-$CH_3OC_6H_4$	+B	50	−0·025	2·08	−1·2
		57	−0·020	1·78	−1·1
α-Naphthyl	−M	33	+0·042	2·93	+1·4
		60	+0·059	2·13	+2·8
α-Naphthyl	+B	26	+0·033	1·78	+1·8
		33	+0·139	4·22	+3·3

[a] The results of duplicated experiments are given.

[b] 2-(p-Anisyl)-cyclopropanecarboxylic acid is known (E. N. Trachtenberg and G. Odian, *J. Amer. Chem. Soc.* **80**, 4018 (1958)). For other acids see Experimental.

[c] Optical rotations were measured in dioxan with a 1 dm cell.

TABLE 3. 2-PHENYLCYCLOPROPANECARBOXYLIC ACID (IIIa) BY THE REACTION OF THE CINNAMATES Ia WITH OTHER REAGENTS

		2-Phenylcyclopropanecarboxylic acid[b]			
Reagent[a]	R*	Yield (%)	α_D[c]	c(g/100 ml)	$[\alpha]_D$
(1)	−M	58	−0·182	2·56	−7·1
(1)	+B	70	−0·056	2·19	−2·6
(2)	−M	25	−0·129	2·08	−9·7
(2)	−M	13	−0·175	2·02	−13·6
(2)	+B	12	−0·070	1·42	−7·3
(2)	+B	12	−0·072	1·79	−6·0
(3)	−M	17	−0·060	2·26	−5·7
(3)	+B	12	−0·055	1·57	−6·9

[a] Reagent (1) means the use of trimethyloxosulphonium iodide and potassium t-butoxide in dimethylsulphoxide, (2) trimethyloxosulphonium chloride and sodium hydride in tetrahydrofuran, and (3) trimethylsulphonium iodide and sodium hydride in dimethylsulphoxide.

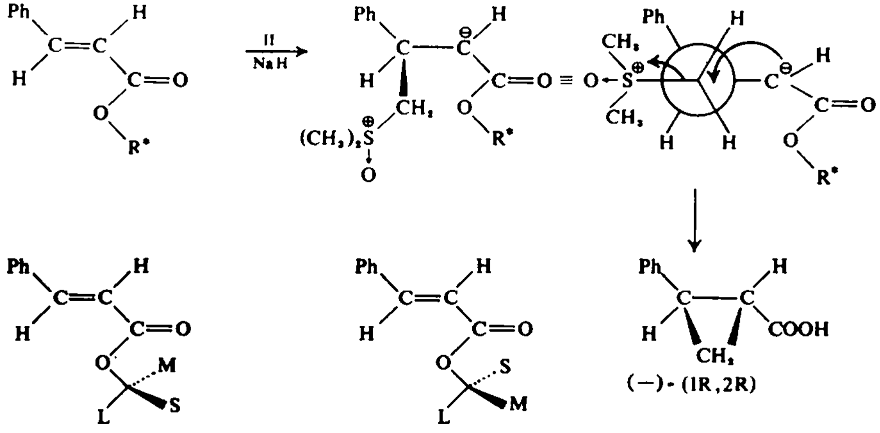
[b] The acidic product obtained by the use of the reagents (2) and (3) was shown to be contaminated with unchanged cinnamic acid (see Experimental). Corrections have been made both for the yields and specific rotations.

[c] Optical rotations were measured in dioxan with a 1 dm cell.

Replacement of trimethyloxosulphonium iodide with the corresponding chloride and the use of tetrahydrofuran as a solvent[3b] results in lower chemical yields. Under similar conditions, using the (+)-bornyl ester (Ia), IIIa is obtained with higher optical rotation than that produced using the iodide in dimethylsulphoxide.

Finally, treatment of Ia with trimethylsulphonium iodide and sodium hydride in dimethylsulphoxide[10] also gives the *laevorotatory* acid (IIIa) with inferior yields in both the (—)-menthyl and (+)-bornyl reactions.

The *laevorotatory* IIIa has the configuration of 1R,2R.[7] It follows, therefore, that the mechanism of the reaction of (—)-menthyl cinnamate with dimethyloxosulphonium methylide or with dimethysulphonium methylide is in accord with the scheme of asymmetric induction as proposed previously for other condensation reactions, namely, *via* the attack of the conformer A from the side of the smallest group S.[11] Certain modifications are, however, necessary when considering the predominant formation of the same (IR,2R)-2-phenylcyclopropane carboxylic acid in the reaction with (+)-bornyl cinnamate. Either the conformation B, *viz.* the *s-trans* conformation of C=C and C=O is wrong, or the attack of sulphur ylides occurs from the side of medium-sized group M rather than the side of the smallest group S. The latter possibility cannot be excluded, as the more effective induction may arise from another asymmetric carbon in the largest group L. Further work is necessary before the problem can be elucidated.



(—)-Menthyl Ester
Conformer A

(+)-Bornyl Ester
Conformer B

EXPERIMENTAL

All temps were uncorrected. Micro-analyses were performed at the Elemental Analyses Centre of Kyôto University. Optical rotations were measured photo-electronically, the smallest reading

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[10] Dimethyloxosulphonium methylide and dimethylsulphonium methylide react stereospecifically and in opposite directions with dihydrotestosterone to give α- and β-oxides: C. E. Cook, R. C. Corley and M. E. Wall, *Tetrahedron Letters* 891 (1965). Rather surprisingly, both reagents gave predominantly the same enantiomer in our reaction.

[11] V. Prelog and H. Scherrer, *Helv. Chim. Acta* **42**, 2227 (1959); H. M. Walborsky, T. Sugita, M. Ohno and Y. Inouye, *J. Amer. Chem. Soc.* **82**, 5255 (1960); H. M. Walborsky, L. Barash, A. E. Young and F. J. Impastato, *Ibid.* **83**, 2517 (1961); H. M. Walborsky, L. Barash and T. C. Davis, *Tetrahedron* **19**, 2333 (1963).

being to ±0·005°. Dimethylsulphoxide was dried with calcium hydride at 60–70° and distilled under red. press.

Starting materials. (−)-Menthyl and (+)-bornyl cinnamates (Ia) were prepared by the reaction of cinnamoyl chloride with (−)-menthol or (+)-borneol at 130°.[6] Methoxy-substituted cinnamates (Ib and Ic) were obtained as follows: a benzene (20 ml) solution of *p*- ór *o*-methoxycinnamoyl chloride (0·05 mole) was added dropwise under stirring to a solution of the respective alcohol (0·05 mole) and pyridine (0·08 mole) in benzene (50 ml) at room temp. After heating the mixture under reflux for 3–5 hr and treatment with water, the cinnamates Ib and Ic were isolated by distillation *in vacuo*. *β*-(α-Naphthyl)acrylates (Id) was prepared similarly. Other data have been summarized in Table 1. Trimethyloxosulphonium iodide,[12] trimethyloxosulphonium chloride[12] and trimethylsulphonium iodide[13] were prepared according to the reported procedures.

2-Arylcyclopropane carboxylic acid from the acrylates (I) *and trimethyloxosulphonium iodide* (II). A mixture of II (4·4 g, 0·02 mole) and NaH (0·48 g, 0·02 mole, or 0·98 g as 50% suspension in mineral oil) in dimethylsulphoxide (40 ml) was stirred at room temp under N_2 during 1 hr. When H_2 evolution had ceased, a solution of I (0·02 mole) dissolved in dimethylsulphoxide (10 ml)[14] was added dropwise. After stirring at room temp for 1 hr and then at 50° for 30 min, the reaction mixture was diluted with water (200 ml) and extracted with ether. The crude ester obtained by evaporation of the solvent was dissolved in 90% EtOH and hydrolysed with excess KOHaq at room temp. After extraction of the neutral fraction[15] with ether, the acidic mixture was purified by extraction with 5% K_2CO_3aq and liberation of III with dil HClaq. The IR spectrum of the crude IIIa (Nujol and CS_2 solution) was identical with that of an authentic sample of *trans*-2-phenylcyclopropane carboxylic acid. Yields and optical rotations of the acids III are given in Table 2.

The analytical sample of 2-(*o-methoxyphenyl*)*-cyclopropane carboxylic acid* recrystallized twice from hexane–benzene (2:1) had m.p. 136–136·5°. (Found: C, 68·52; H, 6·13. $C_{11}H_{12}O_3$ requires: C, 68·73; H, 6·29%.)

The analytical sample of 2-(*α-naphthyl*)*-cyclopropane carboxylic acid* recrystallized twice from hexane had m.p. 122-123°. (Found: C, 79·26; H, 5·81. $C_{14}H_{12}O_2$ requires: C, 79·22; H, 5·70%.)

2-Phenylcyclopropane carboxylic acid (IIIa) *from the cinnamate* Ia *and* II *in the presence of potassium t-butoxide.*[3d] Compound II (4·4 g, 0·02 mole) and powdered potassium t-butoxide (2·3 g, 0·02 mole) were dissolved in dimethylsulphoxide (40 ml) under N_2. The solution was stirred at room temp for 1 hr, when the H_2 evolution subsided. Addition of Ia and treatment of the reaction mixture as before gave the optically active acid IIIa. The properties and yields are given in Table 3.

2-Phenylcyclopropane carboxylic acid (IIIa) *from the cinnamate* (Ia) *and trimethyloxosulphonium chloride.* A solution of trimethyloxosulphonium chloride (3·0 g, 0·024 mole) and NaH (0·6 g, 0·024 mole) in tetrahydrofuran (150 ml) was stirred and heated under reflux in the presence of N_2 until H_2 evolution had ceased completely (5 hr). To a milky suspension of the resulting dimethyloxosulphonium methylide, a solution of (−)-methyl cinnamate (6·8 g, 0·024 mole) in tetrahydrofuran (20 ml) was added during the course of 20 min at room temp. Continued stirring at the same temp for 1 hr and then at 50° for 1 hr followed by isolation of the product yielded an optically active acid. It contained a fair amount of cinnamic acid, as the IR spectrum of the crude acid showed an absorption at 1640 cm^{-1}. However, the formation of IIIa was shown by its optical activity (Table 3) and also by IR absorption at 1020 cm^{-1}. The acid mixture (1·3 g) was treated with diazomethane (0·33 g) in ether. Distillation of the product under red. press. gave an ester mixture (1·3 g), b.p. 136–145°/22 mm. The content of methyl 2-phenylcyclopropane carboxylate was determined by gas chromatography with a high vacuum silicon grease column (2 m) at 200°. The chromatogram indicated the presence of 64–67% methyl 2-phenylcyclopropane carboxylate and 33–36% methyl cinnamate. Their retention times were identical with those of the authentic samples. Calculated yields and specific rotations of 100% cyclopropane carboxylic acid are given in Table 3.

2-Phenylcyclopropane carboxylic acid (IIIa) *from the cinnamate* (Ia) *and trimethylsulphonium*

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[12] R. Kuhn and H. Trischmann, *Liebig's Ann.* **611**, 117 (1958).

[13] H. J. Emeléus and H. G. Heal, *J. Chem. Soc.* 1126 (1946).

[14] If the acrylate I was insoluble in dimethylsulphoxide, tetrahydrofuran-dimethylsulphoxide (1 : 1) mixture (20 ml) was used as solvent.

[15] IR spectrum of this recovered neutral fraction indicated no contamination of any carbonyl compound. Optical rotation of III is, therefore, not attributable to an asymmetric hydrolysis.

iodide.[16] Methylsulphinyl carbanion[3e] was prepared by dissolving NaH (0·5 g, 0·022 mole) in dimethylsulphoxide (40 ml) at 60° under N_2. To this solution, tetrahydrofuran (60 ml) was added in order to avoid freezing. After cooling to 0°, trimethylsulphonium iodide (4·5 g, 0·022 mole) was added. When the iodide had dissolved completely, a solution of Ia (0·020 mole) in dimethylsulphoxide (20 ml) was added at the same temp. Additional stirring at 40° for 1 hr, followed by working up of the reaction mixture as before yielded the impure IIIa, which was esterified with diazomethane in ether. A chromatogram of the ester mixture indicated the presence of 47–51% methyl 2-phenylcyclopropane carboxylate and 49–53% methyl cinnamate.

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[16] Reaction of trimethylsulphonium iodide and ethyl cinnamate gave cyclopropane carboxylate in 10% yield. See Ref. 3*b* and 3*d*.