

Prediction of the Absolute Configuration of Optically Active Pheromones Using Liquid Crystals

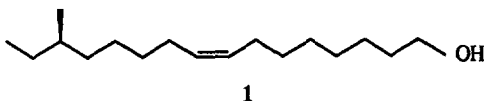
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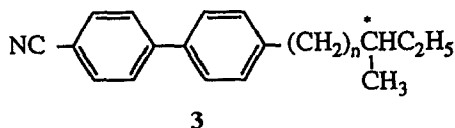
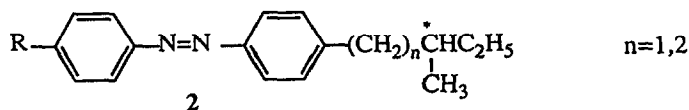
Abstract : Prediction of the absolute configuration of optically active methyl branched pheromones is possible by combining them with mesogens to give them liquid crystalline properties and measuring the helical senses of the chiral nematic phases.

It has been almost impossible to determine the absolute configuration of stereogenic carbons separated from the functional group by physical methods except for X-ray crystallographic analysis. Synthesis has been therefore the only way to establish it. Especially in the pheromone field, stereogenic carbons of some compounds are separated from the functional group. Compound **1** is the first example whose absolute configuration was determined by synthesis.^{1,2}

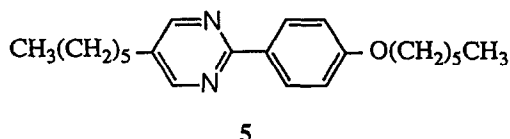
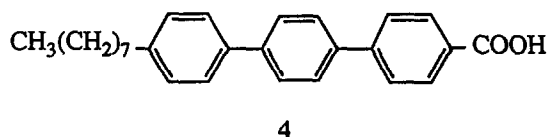


Although some methods using liquid crystals have been tested for the determination of absolute configuration, all the trials were to find the rules simply by doping optically active secondary alcohols or optically active epoxides, which have relatively high twisting power, directly into nematic liquid crystals.³⁻¹⁵ On the other hand, Tsukamoto *et al.* first noticed that the helical senses of the chiral nematic phases for compounds **2** were different between (*S*)-2-methylbutyl derivatives and (*S*)-3-methylpentyl derivatives.¹⁶ Apart from this, Gray and McDonnell found that the helical senses of the chiral nematic phases for compounds **3** reversed depending on whether the number of the carbon atoms *n* was odd or even, and they proposed the odd-even rule for the helical senses of chiral nematic phases.¹⁷

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From these backgrounds, we thought that we would be able to predict the absolute configuration of optically active alcohols by combining them with some particular mesogens to control the arrangement of the chiral groups and measuring the helical senses of the chiral nematic phases. We selected compound 4 as a mesogen, since its esters would tend to have mesogenic properties regardless of the structures of the optically active alcohols and also the alcohols could be recovered by hydrolysis. However, they generally show no chiral nematic phases, and we measured the helical senses of the chiral nematic phases induced by doping 10wt% of the esters into compound 5.¹⁸



Since the twisting power β is regulated by the equation of the intermolecular interaction (eq.1),¹⁹ it is necessary to use the optically active compounds at low concentration or at 100%. (If the chiral compounds are used at high concentration, the helical senses are sometimes reversed.)¹⁹⁻²¹

$$\beta = \chi^2 \beta_{CC} + \chi(1-\chi) \beta_{CC} \beta_{CN}$$

equation 1

χ : concentration of chiral compounds

β_{CC} : interaction between chiral molecules

β_{CN} : interaction between a chiral molecule and an achiral one

Compound 4 was prepared according to the method of Krishnaswamy *et al.*,²² and compound 5 was synthesized according to the method of Zschke *et al.*¹⁸ Chiral alcohols A are all available in our laboratory. Chiral esters B were prepared from 4 and A (Scheme 1).

The results are shown in Table 1. The helical senses reverse depending on the number of carbon atoms from the benzene ring to the stereogenic carbon atom and this method was found to be useful for the prediction of the absolute configurations of optically active alcohols. However, it became difficult to measure the long pitches by a doping method. We thought that we could determine the helical senses even in the case where a functional group was far from asymmetric carbon atoms if the measurements were done with neat chiral compounds. Since the compounds must always show a nematic phase regardless of the kinds of optically active alcohols,²³⁻²⁶ we chose compound **6** as a mesogen. The mesogen **6** was synthesized as shown in Scheme 2, and the Mitsunobu reaction²⁷ was used to connect the optically active alcohols to the mesogen (Scheme 3). The odd-even rule is also applicable in this system.

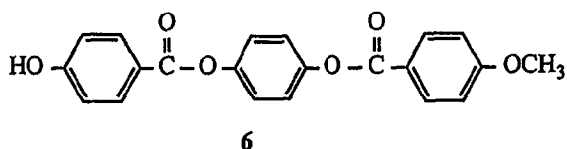
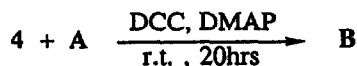


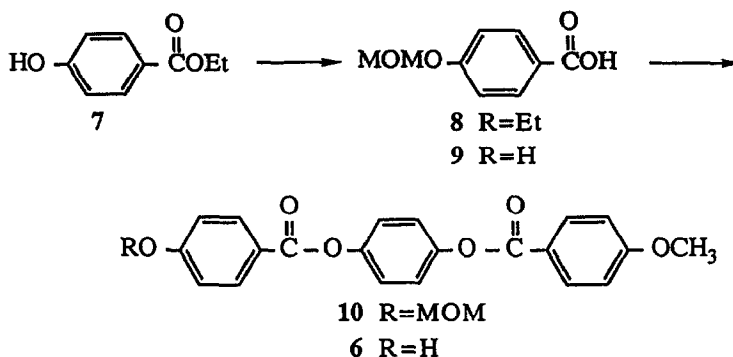
Table 1 Helical senses of chiral nematic phases produced from chiral esters **B** (10wt%) and compound **5** (90wt%) at 50°C and those of chiral nematic phases of chiral compounds **C** at 150°C.

chiral alcohols A	helical senses	
	mixtures of corresponding esters B and compound 5	corresponding ethers C
	left	left*
	right	left
	right	left
	left	right
	left	right
	right	left
	right	left

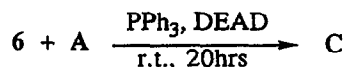
* The chirality was inverted because the Mitsunobu reaction was used.



Scheme 1



Scheme 2



Scheme 3

Table 2 shows the results for the real pheromones synthesized in our laboratory,²⁸⁻³¹ which were converted to the corresponding alcohols and connected to the mesogen 6 to give ethers F by the same method shown in Scheme 3. Even remote asymmetries were sufficiently recognized without exception. In addition, it is noteworthy that only 100 μg samples are needed for measurement.

Table 3 shows the example for pheromones with two asymmetric carbons which were also synthesized in our laboratory.³² The twisting power β is thought to be the sum of those values of the fifth and eleventh asymmetric carbons. That is, the fifth carbon contributes $4.2 \mu\text{m}^{-1}\text{mol}^{-1}$ and the eleventh carbon contributes $0.8 \mu\text{m}^{-1}\text{mol}^{-1}$ to the β value. Consequently the helical sense is decided by the β value of the fifth carbon. This suggests the possibility that this method will be useful for determining the absolute configuration of both asymmetric carbons simultaneously if we measure the β value systematically according to the number of carbon atoms between the functional group and the asymmetric carbon atom and that from the asymmetric carbon atom to the end.

Table 2 Helical senses of chiral nematic phases of chiral compounds F at 150°C.

pheromones D	reagent	corresponding alcohols E	helical senses corresponding ethers F
	LiAlH ₄		left
	1) O ₃ 2) NaBH ₄		left
	1) LiAlH ₄ 2) PO ₂ , H ₂		left
	1) NaOBr 2) H ⁺ 3) LiAlH ₄		left

Table 3 Helical senses of chiral nematic phases of chiral compounds J at 150°C and twisting powers of chiral nematic phases produced from chiral ethers J (10wt%) and compound 5 (90wt%) at 50°C.

pheromones G	reagent	corresponding alcohols H	helical senses	twisting powers β ($\mu\text{m}^{-1}\text{mol}^{-1}$) corresponding ethers J
	1) NaOBr 2) H ⁺ 3) LiAlH ₄		right	3.4
	1) NaOBr 2) H ⁺ 3) LiAlH ₄		right	5.0

In conclusion, we showed that the prediction of the absolute configurations of optically active alcohols is possible by combining them with mesogens to give them liquid crystalline properties and measuring the helical senses of the chiral nematic phase. Remote asymmetries are also recognized sufficiently with a small amount of sample, and this method has been shown to be useful for prediction of the absolute configuration of remote stereogenic centres of pheromones.

Experimental

Determination of the helical senses and the pitch of chiral nematic phases

Although many methods to determine helical senses have been reported,³ we adopted the contact method^{17,33} which is one of the easiest ones. The contact cell (Fig.1) was put on a hot plate having a

thermocontroller. A standard compound of known helical sense was inserted from one side and a compound of unknown helical sense was inserted from another side. If two compounds have the same helical sense, a continuous chiral nematic phase is observed, and if the helical senses are opposite, a noncontinuous band of nematic phase is observed.

For determining the pitch, we used the Cano-Wedge method (Fig.2).³⁴ The tangent of the distance between neighbouring disclination lines gives half the helical pitch.

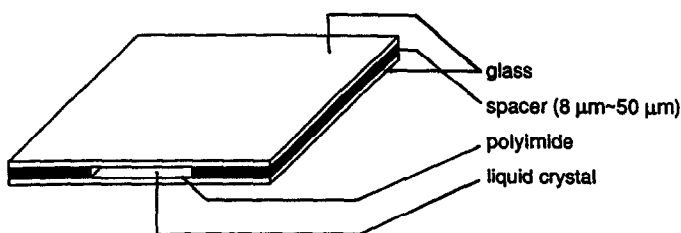


Fig. 1

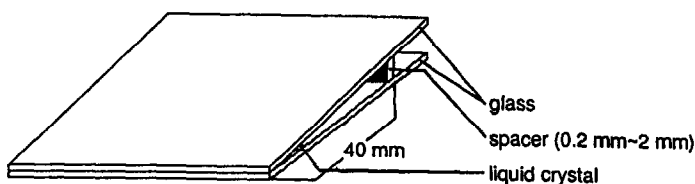


Fig. 2

Preparation of compound 6

MOMCl (2.4g) was added to a stirred and ice-cooled solution of 7 (4.6 g) and *i*-Pr₂NEt (4.4 g) in dry CH₂Cl₂ (20 ml). The mixture was stirred for 1 hr at room temperature. It was poured into an ice-cooled and saturated NaHCO₃ aqueous solution and extracted with ether. The ether solution was washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Elution with *n*-hexane-AcOEt gave 5.10 g (87.6%) of 8, ν_{\max} (neat) 3080(w), 1720(s), 1605(s), 1510(m) cm⁻¹; δ (CDCl₃) 1.42 (3H, t, J=7 Hz), 3.50(3H, s), 4.38(2H, q, J=7 Hz), 5.26(2H, s), 7.07(2H, d, J=8 Hz), 8.01(2H, d, J=8 Hz). (Found: C, 62.55; H, 6.75. Calc. for C₁₁H₁₄O₄: C, 62.84; H, 6.71%).

To the stirred solution of 8 (4.0 g) in EtOH (50 ml) was added 4N KOH aqueous solution (30 ml). The mixture was then stirred for 16 hrs at room temperature. To the stirred and ice-cooled solution was added N-

HCl aq. until the pH of the solution turned to 3. The produced crystals were collected on a filter, washed with water and dried *in vacuo* to give 3.24 g (93.5%) of **9**, m.p. 124°C; $\nu_{\max}(\text{KBr})$ 2700(br), 2550(br), 1675(s), 1605(s), 1510(m) cm^{-1} ; $\delta(\text{CDCl}_3)$ 3.50(3H, s), 5.24(2H, s), 7.11(2H, d, J=8 Hz), 8.06(2H, d, J=8 Hz). (Found: C, 59.33; H, 5.52. Calc. for $\text{C}_9\text{H}_{10}\text{O}_4$: C, 59.33; H, 5.53%).

To a stirred solution of **9** (2.5 g), 4-(4-Methoxybenzoyloxy)phenol²³ (3.3 g) and DCC (1.4 g) in dry CH_2Cl_2 (70 ml) was added DMAP (0.5 g). After the addition, the mixture was stirred for 20 hrs at room temperature. Suspended particles were filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2 (150 g). Elution with CH_2Cl_2 gave 4.78 g (86.6%) of **10**, m.p. 144°C, $T_{\text{NI}} > 230^\circ\text{C}$; $\nu_{\max}(\text{KBr})$ 1730(s), 1610(s), 1605(s), 1515(m), 1505(m) cm^{-1} ; $\delta(\text{CDCl}_3)$ 3.50(3H, s), 3.89(3H, s), 5.26(2H, s), 6.98(2H, d, J=8 Hz), 7.11(2H, d, J=8 Hz), 7.25(2H, s), 8.15(4H, d, J=8 Hz). (Found: C, 67.25; H, 5.00. Calc. for $\text{C}_{23}\text{H}_{20}\text{O}_7$: C, 67.64; H, 4.94%).

To a stirred solution of **10** (2.5 g) in THF (150 ml) was added 6N HCl aq. (60 ml) and the mixture was stirred for 60 hrs at room temperature. The mixture was poured into ice-water (400 ml) and the produced crystals were filtered. The crystals were washed with CH_2Cl_2 and recrystallized from EtOH-AcOEt to give 1.81 g (81.2%) of **6**, m.p. 216°C, $T_{\text{NI}} > 230^\circ\text{C}$; $\nu_{\max}(\text{KBr})$ 3410(br), 1735(s), 1710(s), 1610(s), 1595(s), 1515(m), 1505(m) cm^{-1} ; $\delta(\text{DMSO}-d_6)$ 3.87(3H, s), 6.91(2H, d, J=8 Hz), 7.01(2H, d, J=8 Hz), 7.27(4H, s), 7.97(2H, d, J=8 Hz), 8.07(2H, d, J=8 Hz). (Found C, 68.97; H, 4.47. Calc. for $\text{C}_{21}\text{H}_{16}\text{O}_6$: C, 69.22; H, 4.43%).

General method for the preparation of esters B

To a stirred solution of a chiral alcohol (1 mmol), **4** (1.2 mmol), DCC (1.2 mmol) in dry CH_2Cl_2 (10 ml) was added DMAP (0.3 mmol). After the addition, the mixture was stirred for 20 hrs at room temperature. Suspended particles were filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2 and recrystallized.

General method for the preparation of ethers C, E and J.

To a stirred suspension of **6** (1.2 mmol) and a chiral alcohol (1 mmol) in dry benzene (10 ml) was added $\text{EtO}_2\text{CN}=\text{NCO}_2\text{Et}$ (1.2 mmol) and the Ph_3P (1.2 mmol). After the addition, the mixture was stirred for 20 hrs at room temperature. It was then concentrated *in vacuo* and the residue was chromatographed over SiO_2 and recrystallized.

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