

ABSOLUTE STEREOCHEMISTRIES OF TRANS-2,3-DISUBSTITUTED SPIROCYCLO-
 PROPANE-1,9'-FLUORENE DERIVATIVES: A STYRYL MODIFICATION CD-METHOD
 FOR CARBOXYL SUBSTITUTED CHIRAL CENTERS

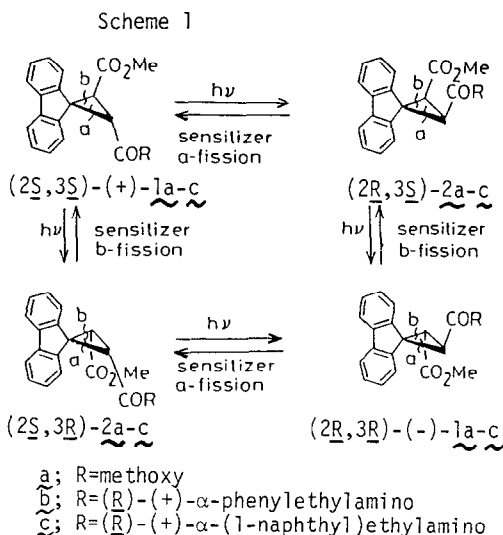
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Summary: Absolute stereochemistries of trans-2,3-disubstituted spirocyclopropane-1,9'-
 fluorene derivatives were determined by both CD and chemical transformation methods. In the
 CD-study, a styryl modification method for carboxyl substituted chiral centers is presented.

In the course of our photochemically induced asymmetric transformation of trans-2,3-di-
 carbomethoxy spirocyclopropane-fluorene derivatives (Scheme 1), where photosensitized cis⇌
trans isomerization of the diastereomeric mixtures gives up to 94% diastereo-
 meric excess of one of the trans-dia-
 stereomers by choice of suitable chiral
 centers (R) and sensitizers,¹ it became
 necessary to determine the absolute
 stereochemistry of the diester (+)-1a.
 We wish here to report the determination
 of the absolute stereochemistry of (+)-
1a and the related compounds by a novel
 application of the CD exciton chirality
 method to di-(E)-styryl chromophore as
 well as by chemical correlation with a
 known compound.

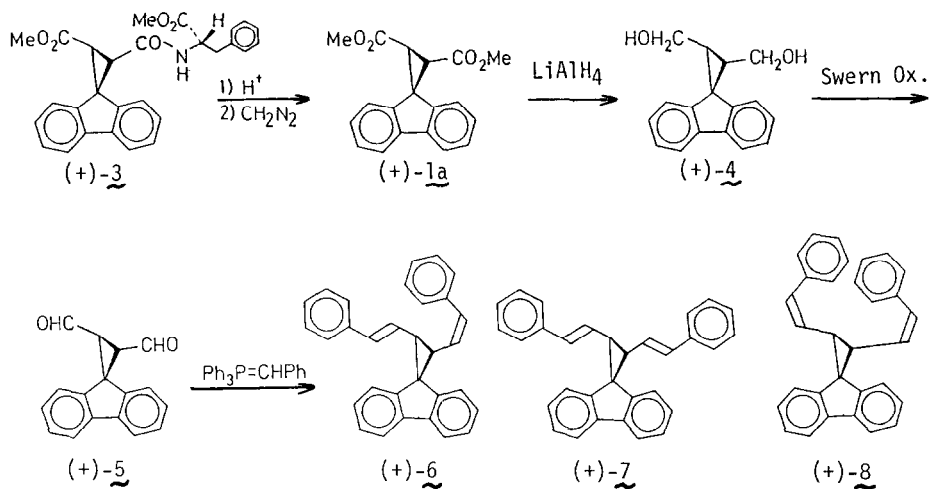


Circular Dichroism (CD) study of trans-2,3-di-(E)-styryl derivative (+)-7

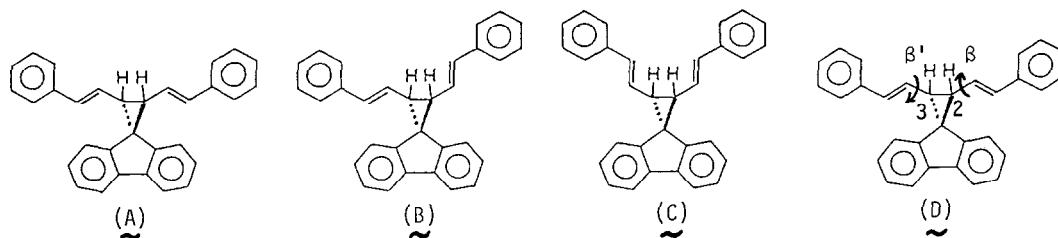
The CD exciton chirality method has proved to be a valuable method for the determination
 of absolute stereochemistries.² A wide applicability of this method has been exemplified in
 the determination of absolute configuration of chiral glycols as has been summarized as the
 dibenzoate chirality rule.² However, such effective application-method for carboxyl substi-
 tuted chiral centers has not yet been established. Application of the CD-method to carboxyl
 groups requires introduction of suitable chromophores in place of carboxyl groups. (E)-styryl
 or phenylethynyl groups seem to be attractive chromophores because of their intense π - π^*
 absorptions and the ease of derivation from carboxyl groups.

Scheme 2 shows the transformation of (+)-1a to trans-di-(E)-styryl derivative (+)-7. Optical resolution of 1 was readily achieved by chromatographic separation (silica gel) of the diastereomeric mixture 3, which had been derived from the corresponding carboxylic acid chloride and L-phenylalanine methyl ester, followed by acidic hydrolysis and esterification with diazo-methane. LAH reduction of (+)-1a ($[\alpha]^{25}_D +340^\circ$ (c 0.5, EtOH)) in THF gave the diol (+)-4 (93% chemical yield; $[\alpha]^{25}_D +39.9^\circ$ (c 0.5, EtOH)) which was then converted into the dialdehyde (+)-5 (89%; $[\alpha]^{25}_D +175^\circ$ (c 0.6, EtOH)) by Swern oxidation.³ Treatment of (+)-5 with benzylidene-triphenylphosphorane in benzene at room temperature gave a mixture of 6 (22% yield), 7 (48%), and 8 (3%). Repeated preparative TLC afforded pure sample of (+)-7 ($[\alpha]^{25}_D +331^\circ$ (c 0.1, EtOH); ¹H-NMR (CDCl₃), δ 3.06 (dd, 2H, J=4.0 and 2.0 Hz), 6.42 (ddd, 2H, J=15.8, 4.0, and 2.0 Hz), 6.66 (d, 2H, J=15.8 Hz), 7.22 (m, 16H), 7.86 (m, 2H)). The UV and CD spectra of (+)-7 are shown in Figure 1. In the CD spectrum the first negative Cotton effect (λ_{ext} 288 nm ($\Delta\epsilon = -27.3$)) and second positive Cotton effect (λ_{ext} 262 nm ($\Delta\epsilon = +75.3$)) are observed.

Scheme 2



The styryl chromophores are most likely to rotate freely around C₂-C_β(C₃-C_β) axes (see D). Therefore, averaged direction of the electronic transition moment of the π-π* absorption of the styryl chromophore will be parallel to the C₂-C_β(C₃-C_β) axes. Providing that the interaction of the electronic transition moment of the two styryl groups is larger than that between the styryl and fluorenyl groups, the first negative Cotton effect suggests that the electronic dipole moment of the two styryl groups are oriented in a left-handed screw, i.e. (2S, 3S) configuration.



Apart from this qualitative consideration, the CD spectrum was theoretically analyzed using π -electron SCF CI dipole velocity MO method.^{2,4} Before the calculation, conformational analysis on the rotation of styryl groups around $C_2-C_B(C_3-C_{B1})$ axes was carried out by the method of molecular mechanics (MMPI) for $(2S, 3S)$ - $(+)$ -**7**. On the symmetrical rotation around the axes, geometrically optimized two conformers **A** and **C** were obtained. Energy difference of the two conformers is calculated to be very small, 0.193 kJ/mol. This small energy difference suggests that the unsymmetrical conformer **B** will be also in an energy minimum. Accordingly, CD spectra were calculated for the three conformers **A**, **B**, and **C** by considering the interaction between two styrene and one fluorene chromophores (Figure 2). In contrast to the UV spectra, the shape of the calculated CD spectra are conformation-dependent. Importantly, however, the sign of Cotton effect is the same in all the three conformers and agrees with the observed CD spectrum of $(+)$ -**7**. The most excellent agreement is seen for the conformer **A** (λ_{ext} 282 nm ($\Delta\epsilon = -24.5$), 253 nm ($\Delta\epsilon = +41.7$)).

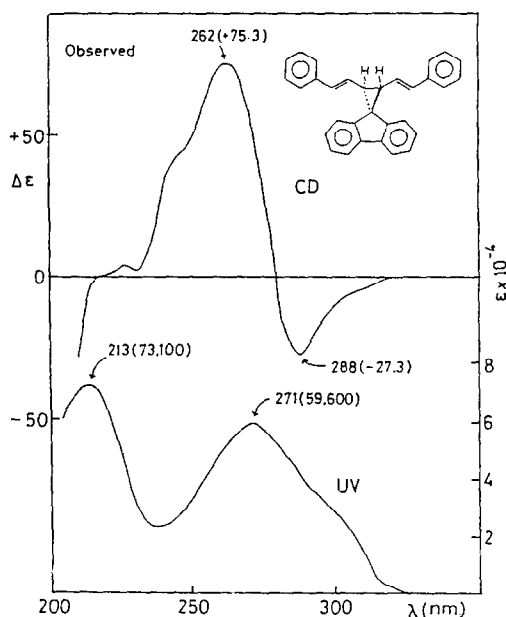


Figure 1. Observed CD- and UV-spectra of $(+)$ -**7**.

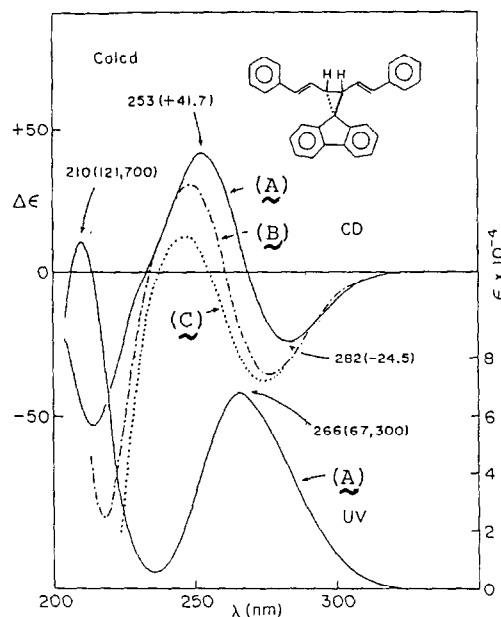


Figure 2. Calculated CD- and UV-spectra for $(2S, 3S)$ -**7**-**(A)**, **(B)**, and **(C)**.

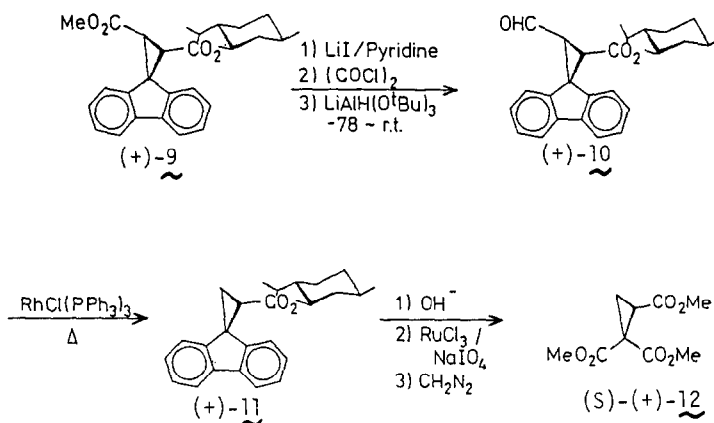
Chemical transformation of $(+)$ -**9** to $(+)$ -**12**

The above CD study reasonably showed $(2S, 3S)$ configuration of $(+)$ -**7**. However, since the experimentally accumulated references for the generality of the chemical modification method are unavailable, experimental confirmation of the theoretical calculation by chemical transformation to molecules having known absolute stereochemistries is essential.

Scheme 3 outlines a successful transformation to known trimethyl 1,1,2-cyclopropane tricarboxylate $(+)$ -**12**. First of all, a diastereomeric mixture of 1-menthyl methyl diester **9** was separated by HPLC into pure form, $(+)$ -**9**, $[\alpha]_D^{25} +164^\circ$ (c 0.1, EtOH), which was correlated with $(+)$ -**1a** by alkaline hydrolysis followed by methylation. Selective demethylation with

LiI-pyridine⁵ (reflux, 6 h), acid-chlorination with oxalyl chloride, and then reduction with $\text{LiAlH}(\text{O}^t\text{Bu})_3$ led (+)-**9** to the aldehyde (+)-**10** ($[\alpha]_D^{25} +119^\circ$ (c 0.3, EtOH)) in 73% overall yield. Decarbonylation of (+)-**10** with Wilkinson's catalyst (1 equiv., xylene, reflux, 16 h) gave (+)-**11** ($[\alpha]_D^{25} +116^\circ$ (c 0.2, EtOH)) in 81% yield. This monoester was degraded to the triester **12** through three-step sequence of alkaline hydrolysis, ruthenium tetroxide-catalyzed oxidation,⁶ and methylation with diazomethane. Gas chromatographic separation of the crude products gave pure known (S)-(+)-**12** ($[\alpha]_D^{25} +121^\circ$ (c 0.4, EtOH); lit $[\alpha]_D^{25} +135^\circ$).⁷ This result establishes the (2S, 3S) absolute configuration of (+)-**1a** and the related derivatives.

Scheme 3



From agreement of the CD-analysis and chemical transformation, we have shown a successful example of the styryl modification method for the determination of absolute stereochemistries of carboxyl substituted chiral centers. In addition, the determination of the absolute stereochemistry of **1** and related compounds should help the use of these compounds as chiral templates in organic synthesis, and such studies are planned.

References

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