

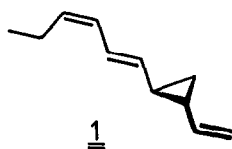
SYNTHESES OF DICTYOPTERENE B (HORMOSIRENE) AND ITS ENANTIOMER
 VIA ASYMMETRIC S_{CN} REACTIONS^{1a}

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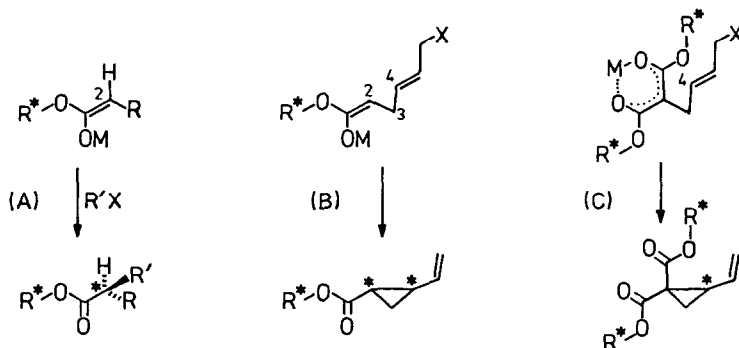
Abstract: Stereocontrolled syntheses of dictyopterene B (hormosirene) (1) and its enantiomer (ent-1) are reported. Key steps are highly stereoselective S_{CN} reactions of esters of alcohols 2 and 5 derived from (+)-camphor.

Dictyopterene B (1), the main constituent of the essential oils from several *Dictyopteris* species, was first isolated by Moore in 1970³. Even at a low level of concentration, this compound displays an intense "ocean smell". More recently, Müller, Jaenicke and their co-workers have detected 1, named hormosirene by them, in a variety of other brown algae, and have shown that it acts as sperm attractant⁴.

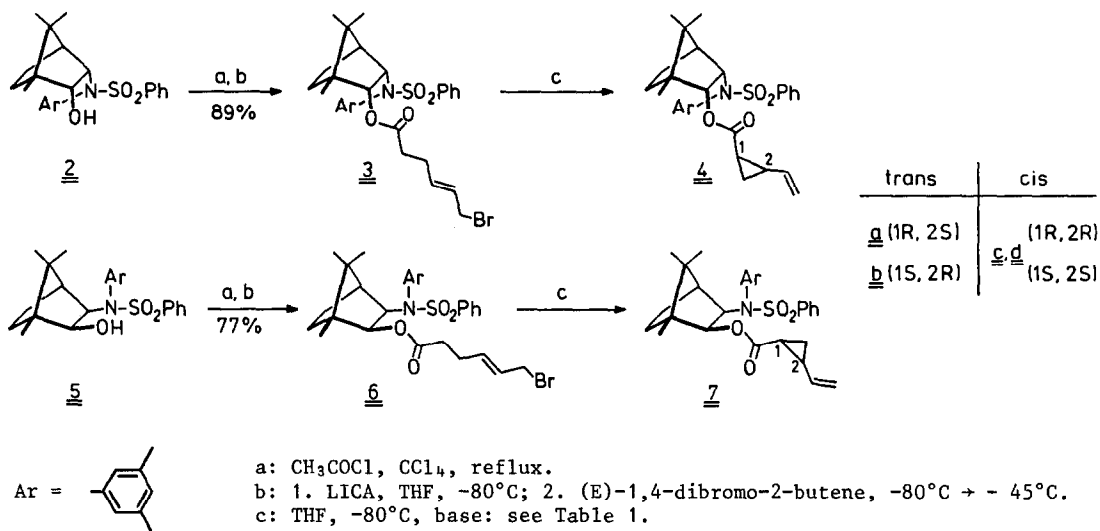


As part of a programme aimed at developing general asymmetric syntheses for 2-vinylcycloalkane carboxylic acids, useful starting materials for natural product syntheses, we have synthesized both dictyopterene B (1) and its enantiomer (ent-1) in high enantiomeric and diastereomeric purity. As we learned after completion of this work, syntheses via a different route have simultaneously been achieved by Jaenicke's group⁵. Previously reported syntheses, usually involving separations of stereoisomers, have yielded racemic⁶ and optically active material of 85% ee⁷.

Key step of our sequence is an S_{CN} reaction of type B, using alcohols 2 and 5 (Scheme 1) as chiral reagents R^*-OH . With these high levels of diastereoselection can be obtained in ester alkylations via lithium enolates according to A, a reaction involving diastereoface selection at center C-2⁸. On the other hand, Quinkert and co-workers⁹ in their highly stereoselective S_{CN} reaction C (R^*-OH = 8-phenylmenthol) have demonstrated the feasibility of effective stereocontrol at the remote center C-4. In view of these examples it was of interest to examine reaction B which involves both centers, C-2 and C-4, and thus allows simultaneous construction of both stereogenic centers of the three-membered ring.



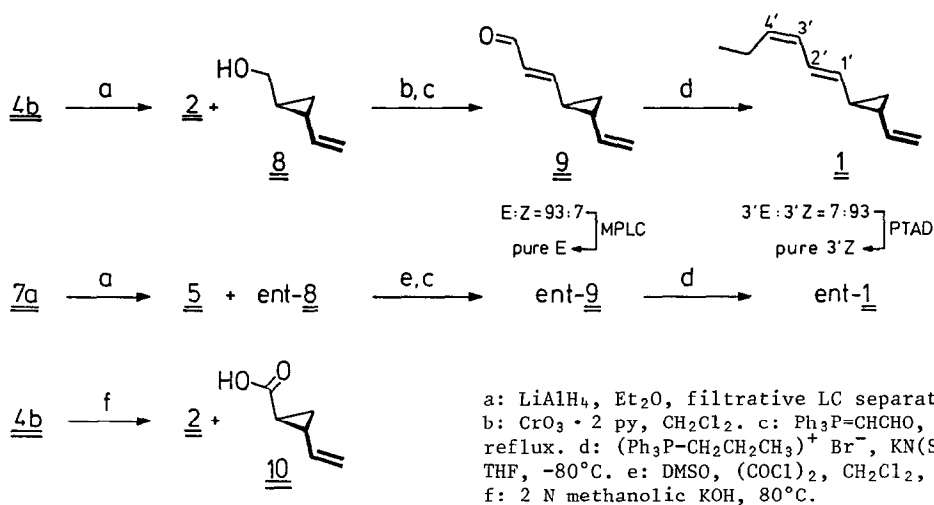
Scheme 1

Table 1. S_{CN} Reactions of Esters 3 and 6

Entry	Ester	Base	<u>4/7</u>				Yield [%] ^{b)}
			<u>a</u>	<u>b</u>	<u>c</u>	<u>d</u> ^{a)}	
1	<u>3</u>	1.2 eq LICA	48	: 48	: 2.5	: 1.5	38 (42)
2	<u>3</u>	1.2 eq LICA/HMPT	33	: 58	: 5	: 4	12
3	<u>3</u>	1.3 eq KO^tBu	14	: 75	: 3	: 12	87 (100)
4	<u>3</u>	3.6 eq KO^tBu + 1.8 eq $\text{H}_2\text{O}^{\text{c)}$	2	: 96.5	: 0.5	: 1	85 (100)
		<u>3</u> cryst.	0.1	: 99.5	: 0.4	: 0	80 (92)
5	<u>3</u>	7 eq KO^tBu + 4 eq $\text{H}_2\text{O}^{\text{d)}$	5	: 92	: 1	: 2	100
		5 cryst.	0.1	: 99.5	: 0.4	: 0	88
6	<u>6</u>	2 eq KO^tBu	74	: 23	: 1.5	: 1.5	82
7	<u>6</u>	4 eq KO^tBu + 2 eq $\text{H}_2\text{O}^{\text{c)}$	83	: 11.4	: 2.8	: 2.8	88
		5 cryst.	99.5	: 0.5	: 0	: 0	59
8	<u>6</u>	7 eq KO^tBu + 4 eq $\text{H}_2\text{O}^{\text{d)}$	92.5	: 7	: 0.2	: 0.3	100
		<u>3</u> cryst.	99.5	: 0.5	: 0	: 0	74

a) Analysis by HPLC. b) Values in brackets: yields corrected with respect to recovered starting material. c) Solid KO^tBu reacted with gaseous H_2O . d) KO^tBu in THF reacted with a solution (7%) of H_2O in THF, -80°C .

Scheme 2



The requisite intermediates 3 and 6 were prepared from 2 and 5 via straightforward 2-step sequences in 89 and 77% yield, respectively (Scheme 1). Their four diastereomeric cyclization products 4a-d and 7a-d, respectively, were found to be separable by liquid chromatography (eluent: petroleum ether/ethyl acetate 95:5, silica gel) which allowed convenient product analysis (HPLC) and isolation of the individual (crystalline) isomers (MPLC). Assignment of relative configuration for the cyclopropane moiety is based on ^1H NMR coupling constants¹⁰; absolute configuration was only established for the trans isomers, by transformation of 4b and 7a into 1 and ent-1, respectively, of known configuration³.

Stereoselectivity of the cyclization reaction was found to be highly dependent on the base system applied (Table 1). Thus, in contrast to previous successful applications in alkylations of type A, lithium cyclohexylisopropylamide (LICA) failed to give satisfactory results upon reaction with 3 (entries 1,2). Of other bases then investigated for the cyclization of 3, KO^tBu (THF) proved most successful (entries 3-5), but showed properties dependent on the degree of purity. Thus, a partially decomposed sample gave a higher level of diastereoselection than the freshly sublimed pure compound. Following this lead, we then used various mixtures obtained by controlled addition of water to pure KO^tBu ¹¹. Finally, conditions as specified by entry 4 of Table 1 produced the isomer 4b with excellent diastereoselectivity¹². As anticipated on the basis of prior experience⁸, the exo isomer 6 behaved similarly to 3 and, also expected, preferentially gave the isomer 7a with absolute configuration of the cyclopropane moiety opposite to that of 4b.

Cyclizations on a 10 g scale followed by recrystallization afforded the cyclopropane derivatives 4b and 7a 99.5% pure¹³ in 74-92% yield. Saponification of 4b (Scheme 2) gave the known⁷ carboxylic acid (+)-(1S,2R)-10, $[\alpha]_{\text{D}}^{26} = +194$ ($c = 1.3$, 95% EtOH), $[\alpha]_{\text{D}}^{26} = +178$ ($c = 1.1$, EtOH)⁷, in 74% overall yield from 2. Alternatively, reductive ester cleavage of 4b and 7a followed by filtrative LC separation of products gave the alcohols 8 and ent-8 in overall yields of 87 and 49% from the reagents 2 and 5, respectively; 8: $\alpha_{\text{D}}^{25} = +61.2$ (neat, $d = 1 \text{ dm}$)¹⁴, $[\alpha]_{\text{D}}^{26} = +60.1$ ($c = 1.0$, 95% EtOH), $[\alpha]_{\text{D}}^{26} = +54$ ($c = 1$, EtOH)⁷; ent-8: $\alpha_{\text{D}}^{25} = -60.5$

(neat, $d = 1$ dm)¹⁴; as the reductive ester cleavage cannot cause racemization, enantiomeric purities of 8 and ent-8 must be identical to the diastereomeric purities of the precursors¹³, i. e. 99.8 and 99.0% (Table 1), respectively.

For transformation of the alcohols 8 and ent-8 into the target compounds stereoselective Wittig olefination methods worked out by Bestmann and co-workers¹⁵ (Scheme 2) were used. The requisite aldehydes were obtained by Collins¹⁶ or Swern¹⁷ oxidation. Their reaction with the phosphorane $\text{Ph}_3\text{P}=\text{CHCHO}$ afforded the enals 9 and ent-9 as 93 : 7 E/Z mixtures (HPLC analysis). MPLC purification gave the pure E isomers in 52 and 32% yield from 8 and ent-8, respectively; 9: $[\alpha]_D^{25} = +230$ (neat, $d = 1$ dm)¹⁴. Finally, reaction with the "salt-free" phosphorane $\text{Ph}_3\text{P}=\text{CHCH}_2\text{CH}_3$ yielded 1 and ent-1 as 93 : 7 3'Z/3'E mixtures (GLC analysis¹⁸). The 3'E isomers were selectively removed by reaction with 4-phenyl-1,2,4-triazolidine-3,5-dione (PTAD) (CH_2Cl_2 , -80°C)¹⁹ to give pure dictyopterene B (1) and its enantiomer in yields of 59 and 50%, respectively; 1: $[\alpha]_D^{24} = -41.6$ ($c = 0.53$, CHCl_3), $[\alpha]_D^{24} = -43$ ($c = 10$, CHCl_3)³; ent-1: $[\alpha]_D^{24} = +41.3$ ($c = 0.67$, CHCl_3).

According to evaluation by experts (BASF AG), olfactory properties of 1 and ent-1 differ considerably. In particular, only 1 displays the characteristic very intense, rather pleasant, "ocean smell". The odour of ent-1 is less intense and devoid of this note.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

- (a) The work described here was presented in several lectures (G. H.), first at the "Heidelberger Chemische Gesellschaft", 14 February 1984. (b) Undergraduate research participant, March/April 1984 (preparation of ent-1 from 5).
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- Trans isomers 4a,b and 7a,b: $J_{1,2} = 4.1 \pm 0.1$ Hz; cis isomers 4c,d and 7c,d: $J_{1,2} = 8.5$ Hz.
- KOH does not effect cyclization of 3.
- Control experiments showed that under the reaction conditions KO^tBu does not induce epimerization at C-1; i. e. the reaction is kinetically controlled.
- If desired, 4b and 7a may be obtained pure by additional recrystallization steps and/or MPLC.
- Not normalized with respect to density.
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- GLC: quartz capillary column 25 m \times 0.32 mm, coated with DB 5, inj. temp. 200°C, column temp. 50°C.
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(Received in Germany 15 April 1985)