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SYNTHESIS OF (+) DICTYOPTERENE A CONSTITUENT OF MARINE BROWN ALGAE and (+) DICTYOPTERENE C' BY CHIRALITY TRANSFER OF OPTICALLY ACTIVE ALLYLIC BENZOATE WITH PALLADIUM (O) CATALYST.

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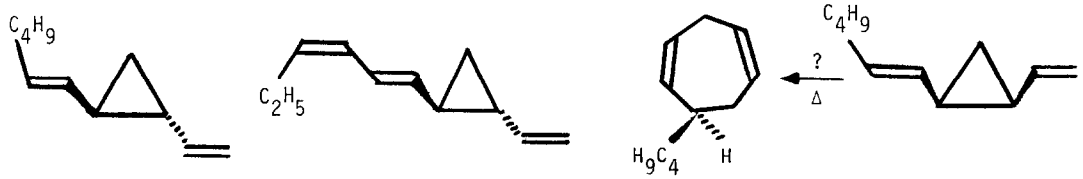
Abstract : The first enantioselective syntheses of (+) dictyopterene A 1 and (+)dictyopterene C' were reported.The key reaction was based on palladium promoted cyclisation of chiral allylic benzoate 5 with transfer of chirality (anti attack of the palladium with respect to the leaving group) to give optically active vinylcyclopropane 7 with (R) configuration which contains proper functionality for further elaboration into 1 and 3

Dictyopterene A (+)-(R,R)-trans-1-(E-hex-1'enyl)-2-vinylcyclopropane 1 Dictyopterene B(2) and Dictopterene C'(-)-(R)-6 butylcyclohepta-1,4-diene 3 have been isolated by R.E Moore from Hawaian Seaweed belonging to genus dictyopteris [1]. These compounds exhibit remarkable physiological activities [2].



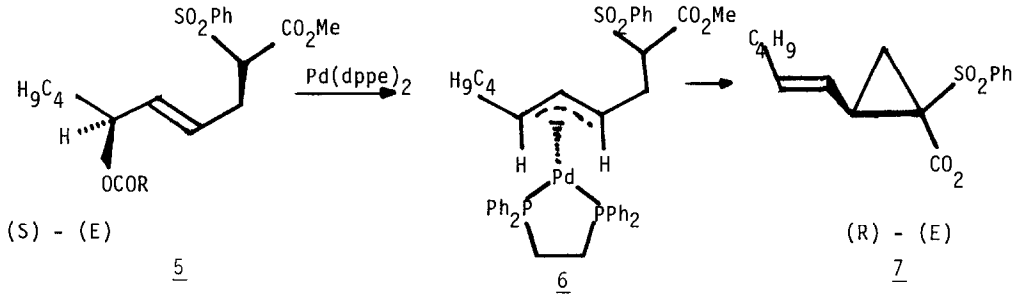
1 2 3 4

Previous synthetic approaches to 1 and 2 have involved functionalization of cyclopropane dicarbaldehyde[3] using a Wittig reaction. A recent and efficient stereoselective synthesis of dictyopterene B 2 has been developed[4] . No enantioselective synthesis of natural (+) dictyopterene A 1 and dictyopterene C' 3 have been so far described.

In this paper we report the first enantioselective syntheses of(+) dictyopterene A[5] 1 and (+) dictyopterene C'[5]. The strategy is outlined in Scheme I. We used the palladium promoted SN'_2 cyclization of functionalized allylic substrates 5 into cyclopropane 7 by the method developed in our laboratory[6] .

The reactions of allylic derivatives have been investigated for many years [7]mainly in terms of stereochemistry. The palladium[8] catalyzed reaction would be valuable in the tranfer [9] of C-O chirality of 5 to the newly formed C-C bond in the vinylic cyclopropane 7. The success of this cyclisation required the functionalized chiral allylic benzoate 5 with (S) configuration [16](Scheme I). This strategy involves the following steps : (i) the palladium attacks the double bond of the allylic substrate opposite to the leaving benzoate group, with formation of chiral palladium species 6 (ii)The nucleophile attacks from the face of the η^3 allyl opposite to the palladium[9]. The process allows a net SYN, SN'_2 replacement of the benzoate by the C-C bond in the cyclopropane 7.

Scheme I

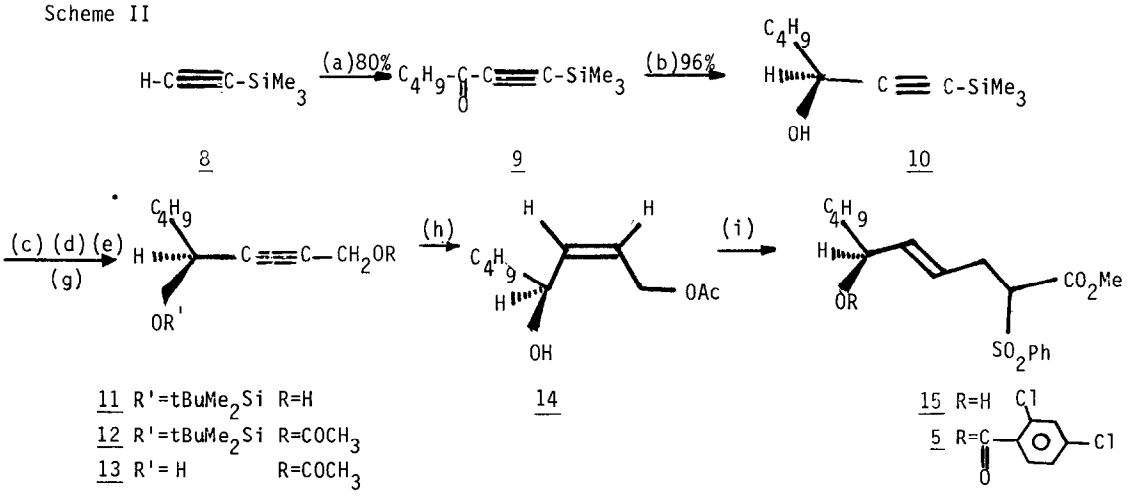


(S) - (E) 5 6 (R) - (E) 7

The key functionalized allylic benzoate 5 is readily prepared in a few steps $(\alpha)_D$ = + 9.37° (C = 2.86 in ether) with 85% e/e ,from commercially available[10] trimethyl silyl acetylene 8 (Scheme II).

Lithiation of 8 with bulylithium in ether -20°C, transmetallation[11] with manganous iodide, followed by treatment with pentanoyl chloride leads to the silylated ketone 9. Reduction of 9 according to the Midland procedure [12] with (S) Alpine Borane [13] gave the allylic alcohol 10 with (S) configuration $(\alpha)_D$ = - 12.03° (C=3.2 in ether). Removal of the silyl group in 10 is accomplished with tetrabutylammonium fluoride in THF and gave(S)hept-1-yn-3ol(85%ee):$(\alpha)_D$= -16.15°(c=3.3 in dioxanne (litt [12] (α) 25_D max= -19° (C-3.3 in dioxanne) . This alcohol is readily converted (ter-butyldimethylchlorosilane, imidazole, DMF, 25°) into its ter butyldimethylsilyl ether ($\alpha)_D$= -35° (C=3.32 in ether) . The hydroxymethylation is accomplished by treatment of the protected chiral ether with one equivalent of ethyl magnesium bromide and gazeous formaldehyde wich produced 11 (α) =-38.35° (C = 3.17 in ether) Scheme II.

Scheme II



8 9 10

11 R'=tBuMe2Si R=H
12 R'=tBuMe2Si R=COCH3
13 R'= H R=COCH3

14

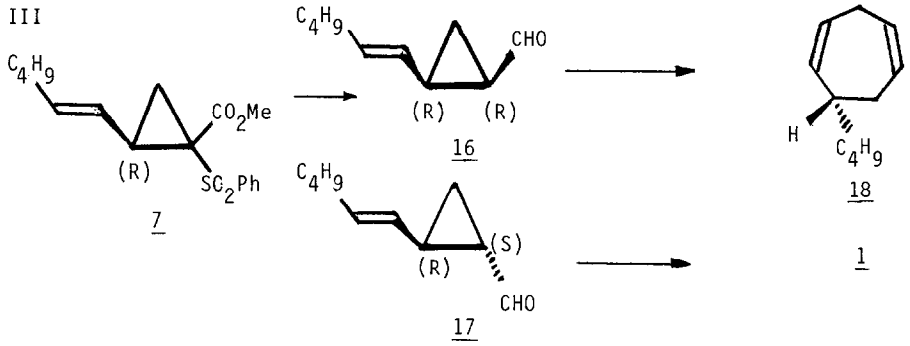
15 R=H
5 R=

(a) Buli (ether -20°C), then Mn I_2 (1.1 eq) ; C_4H_9COCl ;(b) (S) Alpine Borane, THF , 48 h, RT; (c) (Bu)4 N^+ F^-, THF 1 h,Rt ; (d) $tBuMe_2SiCl$, Imidazole, DMF,1h 25°C ; (e) EtMgBr,DMF then H_2CO,2 h,Rt ; (f) AC_2O,DMAP,NEt_3 in CH_2Cl_2, 20mn , RT ; (g) (Bu)$4N^+F^-$, THF, 1h 30 RT, (h) Pd / Lindlar /H_2 /in MeOH ; (i) Ph $SO_2CH_2CO_2Me$,DBU, 1.1eq ; Pd(dppe)2 5%, 1h 15, 25°.

Acetoxylation of 11 in methylene chloride gives 12 (α) = - 29.05°(C =3.07 in ether). Desilylation of 12 using $(Bu)_4N^+F^-$ in THF produces 13,(α)D = -10.3°(C = 2.98 in ether). Semihydrogenation of 13 afforded 14 (α)D= -11.26) (C = 3.06 in ether) The critical alkylation[15] of 14 is achie ved with methyl benzenesulfonylacetate ,DBU, 5% of Pd (dppe)2; THF, 5mn ,25°C) and proceeded smoothly yielding to 15 (α)D = 0.83°(C = 3.47in ether). The key intermediate 15 is obtained[15] in 23% overall yield from 10 after purification by flash chromatography, now 15 contains the carbon skeleton for cyclopropanation reaction . Intramolecular palladium cyclisation is cleanly effected from the benzoate 5 essentially as previously reported[6] . It is noteworthy that the desired E stereochemistry[16] of the double bond was obtained in the resulting cyclized product. (Scheme III).

Final elaboration of vinylic side chain is carried out from 60/40 ratio of the aldehydes (α) 16+17 (α)D = + 60.2° (C=3 in ether) which are obtained after desulfonylation (Na/Hg,Na_2HPO_4,RT) reduction of the esters (DIBAL) in THF followed by oxidation (pyridinium chlorochromate in CH_2Cl_2).

Scheme III



The aldehydes 16(R,R) and 17 (R,S) respectively are useful precursors of dictyopterenes A and C' by Wittig reaction . It is thought that dictyopterene C'(3) arises from Cope rearrangent in vivo of 4 (which has not been found in the essential oil). [19]. Treatment of these two chiral aldehydes 16 and 17 afforded [17] the natural[5] (+) dictyopterene A (1) (α)D = +59.75(C=0.82 in $CHCl_3$);83% ee and the unatural (+) dictyopterene C' 18,(α)D= + 10.2°(C=0.9 in CHCl3);85% ee.

In summary we present here the first enantioselective synthesis of natural (+) dictyopterene A 1 with **complete chirality transfer** of allylic benzoate promoted by palladium (0) catalyst.Simultaneous synthesis of (+) dictyopterene C' clearly shows that (1R,2S) cis divinylcyclopropane 4 (which does not occurs in nature) cannot be the biosynthetic intermediate of (-) dictyopterene C'(3) by thermal Cope rearrangement. From this work the experimental verification of the biosynthetic hypothesis[18]is possible. This study is currently in progress.

ACKNOWLEDGMENTS Financial assistance and grant for F.C. (1982-1985) from the centre National de la Recherche Scientifique (CNRS) are gratefully acknowleged.

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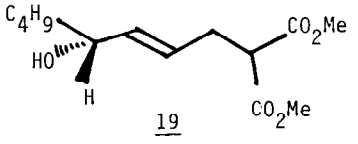
15) With Sodio methylbenzenesulfonylnylacetate, substantial amount of dialkylation was obtained under the same condition. Howewer we found that with D.B.U. as base the monoalkylation proceded in good yield (70%)

15 IR (film) 3450,2930,2860,1740,1440,1315cm-1. NMR (80 MHz, CDCl3) 0.6 - 1,8(m, 9H) 2.52-2.90 (m,2H), 3.7 (s,3H), 3.82 - 4.25 (m,2H), 5.4 - 5.75 (m,2H) , 7.5 - 8.12 (m 5H).

16) The utilisation of 2,4 dichlorobenzoate as leaving group in the catalyzed process gave good yield 80% . For an elegant **un**catalyzed chirality transfert,see : G.Stork and A.R. Schoofs, J.Amer.Chem.Soc.101 5081 (1979).In our case **uncatalyzed** process gave poors yields (10-15%). Preliminary alkylation of sodiomethylmalonate with enantiomeer of 14 gave 19 its cyclisation afforded 20 (α)$_D$ = - 6.47° with 90% of chirality transfer by NMR with schift reagent : tris 3- (hepta fluoropropylhydroxymehylene) d camphorato Europium (III)



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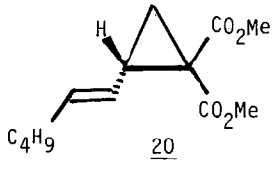

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19(α)$_D$= -31.53° (C=3 in ether);IR (film)3450,3000,2930,2950,1730,1430,cm^{-1};NMR (80MHz CDCl3) 0.7 - 1.75 (m,9H); 2 (OH) ;2.50 - 2.82 (m,2H);3.5 (t,1H);3.8 (s,6H);3.82 - 4.25 (m,1H); 5.6 - (m,2H);5.8 (m,2H).

20 (α)D = - 6.47 (C = 2.47 in ether). IR (film) 3020,1730,1450 cm-1;NMR ($CDCl_3$ 250 MHz)0.88(t,3H);1.15-1.45(m,4,H);1.5-1.6(m,1H);1.65-1.95(m,1H);2(q,2H);2.5(q,1H);3.75(s, 6H);4.98- 5.13 (m,1H ^3J =15,2 Hz,^3J=8Hz); 5.63-5.8(m, 1H ^3J=15.2 Hz,^3J=6Hz).

7IR(film)2960,2940,2860,1730,1440,1320cm-1.NMR($CDCl_3$)0.62-1.5(m,7H);1.62,2.35(m,4H);2.6-3.12 (dd ,1H);3.62(s,3H);4.99-5.5(m,1H);5.5-6.12(m,1H);7.2-8.2(m5H).

17) all spectroscopic data IR;M.S;NMR (80MHz)of 1 and 18 (separated by preparative G.C)were identical with these published[1]by R.E.Moore on natural products . The NMR of 1 recorded at (500 MHz) Brucker revealed 10% of material with Z stereochemistry.

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