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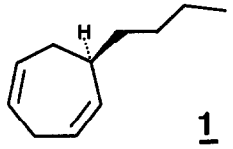
ENANTIOSELECTIVE SYNTHESIS OF DICTYOPTERENE C
6R-(-)-BUTYL-2,5-CYCLOHEPTADIENE
THE PHEROMONE OF SEVERAL DICTYOTALES (PHAEOPHYCEAE)

Theo Schotten, Wilhelm Boland and Lothar Jaenicke*)

Institut für Biochemie, An der Bottmühle 2, D-5000 Köln 1, FRG

Abstract: R-(-)-Dictyopterene C (1) is a widespread constituent of many marine brown algae (Phaeophyceae). A highly enantioselective synthesis of 1 and its enantiomer ent-1 via chromatographic separation of the diastereomeric *p*-hydroxyphenylethylamide intermediates 3a and 3b is described.



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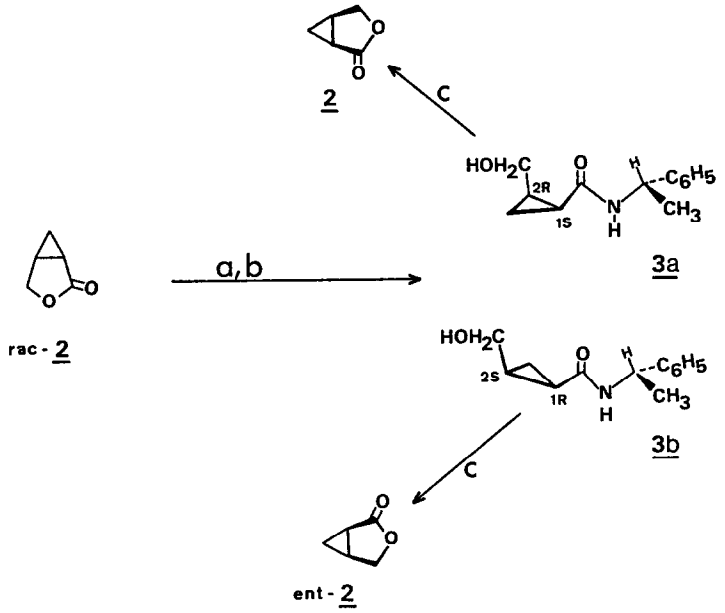
(R)-(-)-Dictyopterene C 1 and several other unsaturated C_{11}-hydrocarbons were first isolated by R.E. Moore et al. from the Pacific seaweeds Dictyopteris plagiogramma and D. australis collected around Hawaii[1,2]. Its occurrence in several North-Pacific representatives of the same genus was also reported by Kajiwara et al.[3]. The absolute configuration of 1 was established as (6R)- by ozonolytic degradation of R-(-)-1 to S-(-)-butylsuccinic acid[2]. R-(-)-1 was later identified by Müller et al. as the sperm attractant of female gametes of the North Atlantic phaeophyte Dictyota dichotoma[4]. Very recently we found that dictyopterene C is also the major product of the egg secretions of the Australian phaeophyte Dictyota prolifera[5]. The very small amount of isolated material (ca. 5 µg) did not allow for the determination of its absolute configuration. Hence, we approached this question by synthesizing 1 and ent-1 and to eventually compare their pheromone activity for male gametes of Dictyota prolifera.

A promising route to R-(-)-1 of very high optical purity is the chromatographic separation of suitable *p*-hydroxyphenylethylamide intermediates according to the method of Helmchen[6], which also allows the inherent control of the optical purity of the products obtained[7].

Synthesis was started with the readily available lactone[8] rac-2 which forms the two diastereomeric amides 3a and 3b in 80% yield, if reacted with 2 eq. S-(-)-phenylethylamine and 1 eq. 2-hydroxypyridine[6] as depicted in Scheme 1. Both diastereomers are easily separated by MPLC on silica gel (ca. 400 g silica gel loaded with the amide mixture in 1 g aliquots and eluted with hexane/-AcOEt 1:9/v:v; $\alpha = 1.45$).

Scheme 1



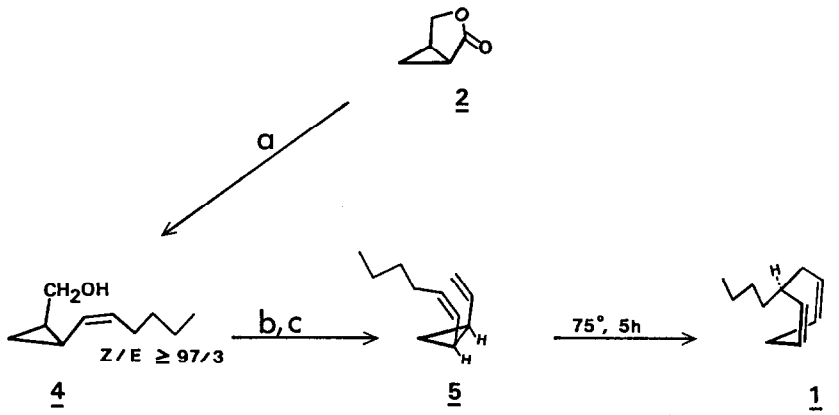
a) 2 eq. S-(-)-phenylethylamine and 1.1 eq. 2-hydroxypyridine
b) separation, see text
c) 2 N H_2SO_4 in dioxane/water (1:1), 12h, 90°

The "anti" orientation of the aromatic ring and the cyclopropyl moiety in (-)-(1S,2R)-3a, diminishes its diastereoselective interaction with the stationary phase; therefore this amide elutes first[7,10] $[\alpha]_D^{25}$ = -151.4 (c = 3.7, MeOH; 83% yield), clearly separated from (-)-(1R,2S)-3b[10] $[\alpha]_D^{25}$ = -153.3 (c = 3.98, MeOH; 55% yield). After recrystallization from AcOEt both compounds were obtained diastereomerically pure[9] as confirmed by HPLC on an analytical column. Support for this configurational assignment comes also from the known absolute configurations of the products 2[11] and 1[2].

Mild acid hydrolysis[6] (2N H_2SO_4 in dioxane/water (1/1; v/v), 16 h, 90°) of 3a or 3b furnished the two key intermediates 2 $[\alpha]_D^{25}$ = -69.5 (c = 6.8, $CHCl_3$), $[\alpha]_D^{25}$ = -61.8 (c = 6, $CHCl_3$)[11] and ent-2 $[\alpha]_D^{25}$ = +68.7 (c = 4.6, $CHCl_3$); both in 97% yield.

From the two optically pure lactones both enantiomers of dictyopterene C, 1 and ent-1, respectively, are readily synthesized as outlined in Scheme 2. Reductive olefination[12] of 2a with 1.1 eq. diisobutylaluminium hydride in toluene at -78°, followed by immediate addition of a "salt free" preparation of $Ph_3P{=}CH(CH_2)_3CH_3$ in THF according to Bestmann et al.[13] gives the alcohol 4,

Scheme 2



a) 1.1 eq. DIBAH at -78° in toluene, followed by addition of 1.5 eq. "salt free" $CH_3(CH_2)_3CH=P(C_6H_5)_3$, then warm up to r.t., cf. ref. 12.
b) Pyridiniumchlorochromate
c) $CH_2=P(C_6H_5)_3$ in THF

$[\alpha]_D^{25}$ = -81.2 (c = 2.6, CH_2Cl_2) in 45% yield and ~97% stereochemical homogeneity[10,14]. By subsequent oxidation of 4 with pyridiniumchlorochromate and Wittig reaction of the intermediary aldehyde with $Ph_3P=CH_2$ the already known dictyopterene A isomer[15] 5, $[\alpha]_D^{25}$ = -117,6 (c = 2.4, CCl_4) is obtained in 53% overall yield. Upon heating to 75° for five hours in a sealed vial 5 rearranges in almost quantitative yield to dictyopterene C 1 $[\alpha]_D^{25}$ = -15,5 (c = 1.74, $CHCl_3$), $[\alpha]_D^{22}$ = -12 (c = 7.32, $CHCl_3$)[2]. Since this sigmatropic Cope rearrangement is known to proceed stereospecifically over a cis-endo transition state[16], the optical purity of synthetic 1 only depends on the stereochemical purity of the alcohol 4 which was found to be ~97% Z; accordingly also 1 will have 97% enantiomer excess. Hence, the optical purity of the dictyopterene C isolated by Moore et al.[2] was not more than ca. 75%.

By the same route, ent-2 was transformed into ent-1 $[\alpha]_D^{25}$ = +15.1 (c = 0.69, $CHCl_3$) via the alcohol ent-4 $[\alpha]_D^{25}$ = +80.0 (c = 2.2, CH_2Cl_2) and the dictyopterene A isomer ent-5 $[\alpha]_D^{25}$ = +115.3 (c = 0.89, CCl_4).

Comparative biological activity tests on male gametes of Dictyota prolifera with 1 and ent-1 are currently under investigation. Interestingly, male gametes of Ectocarpus siliculosus, which respond enantioselectively to the structurally related pheromone ectocarpene (6S-(+)-(1Z)-butenyl-2,5-cycloheptadiene)[17] are unable to distinguish between 1 and ent-1. Their receptor obviously directionally recognizes the π-electron system of the extra double bond within the butenyl-substituent.

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8. Racemic lactone **2** is most conveniently prepared by $NaBH_4$-reduction of the corresponding cyclopropyldicarboxylic acid anhydride.

9. Enantiomerically pure S-(-)-phenylethylamine $[\alpha]_D^{25}$= -40.34 (neat; e.e. = 99.95%), cf. ref. 6, was used.

10. Spectroscopic data of new compounds: **3a**: ^1H NMR (CCl_4):0.68-1.73 (m,4H,cyclopropyl, sek. and tert.-CH); 1.40 (d, CH_3, J=8.3); 3.60-4.05 (ABX-syst.,CH_2OH: J_{AX}=6.7, J_{BX}=7.3, J_{AB}=13.3); 4.03 (s,OH); 5.03 (qi., $CH(CH_3)C_6H_5$); 7.28 (s,C_6H_5); 7.20 (d,-NH-). - **3b**: 0.78-1.72 (m,4H, cyclopropyl, sek. and tert.CH); 1.43 (d,CH_3, J=7.3); 3.40 (s,OH); 3.43-3.98 (ABX-syst.,CH_2OH: J_{AX}=5.0, J_{BX}=8.3, J_{AB}=13.3); 5.70 (qi., $CH(CH_3)C_6H_5$); 6.75 (d,NH); 7.30 (s,C_6H_5). - **4**: 0.31 (qu., 1H,sek.-cyclopropyl); 0.93 (t,CH_3); 0.70-1.10 (m, 1H, sek.-cyclopropyl); 1.10-1.80 (m,6H,CH_2 and tert.-cyclopropyl); 1.85-2.35 (m,CH_2CH=CH); 2.45 (s,broad,OH); 3.22-3.75 (m,CH_2OH); 4.90-5.70 (m,CH=CH). - MS (70 eV): **3a** or **3b**: 219 M^+(3), 204(1), 188(21), 163(10), 120(56), 106(51), 105(100), 79(26), 77(38), 59(18), 55(47), 43(27). - **4**: 154 M^+(2), 136(2), 123(3), 110(5), 107(4), 93(13), 81(50), 79(43), 77(18), 67(100), 55(32), 54(33), 41(67), 39(31). All new compounds gave satisfactory microanalyses.

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14. Alcohol **4** is homogeneous to GC. The only evidence for a small trace (ca. 3%) of an E-contaminant was the ^1H NMR of **5**.

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