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SYNTHESIS OF OPTICALLY ACTIVE NATURAL CAULERPOL

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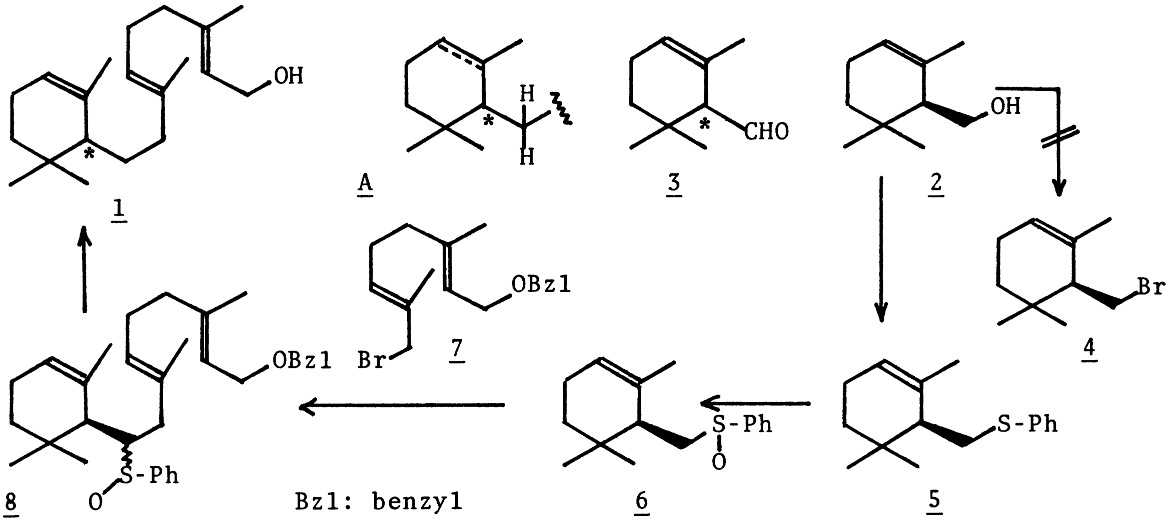
Synthesis of caulerpol (1) from (S)-(-)-α-cyclogeraniol (2), determining the absolute configuration of the asymmetric center is reported.

Caulerpol (1)[1)] is an optically active diterpene alcohol isolated from a marine algae, *Caulerpa brownii* and was reported as the first compound with retinol carbon skeleton from plant sources. Although a synthesis of the racemic form of 1 was reported,[2)] the absolute configuration of the asymmetric center (*) remained undetermined. We describe here the first synthesis of optically active natural caulerpol (1) from easily available (S)-(-)-α-cyclogeraniol (2), determining (S)-configuration of the asymmetric center (*). Although several successful syntheses of physiologically active terpenes have been reported[3)] using optically active α-cyclocitral (3) as a versatile key intermediate for asymmetric α-cyclogeranyl portion, no attempt to employ optically active α-cyclogeraniol (1 or its enantiomer) for such purpose has been made, which seems to be more useful than 3 for syntheses of cyclic terpenes possessing the partial structure (A). We intended to investigate the utility of 2 for syntheses of the class of terpenoids mentioned above. Caulerpol (1) seemed to be the simplest attractive synthetic model for such intention.

Optically active (S)-(-)-α-cyclogeraniol (2), $[\alpha]_D^{30}$ -115°(EtOH), was obtained by the known procedure from α-cyclogeranic acid.[3a)] In order to realize carbon-



Bzl: benzyl

carbon bond formation, transformation of 2 to the bromide (4) or the sulfide (5) was investigated. Unfortunately the bromination of 2 with PBr$_3$ or CBr$_4$-Ph$_3$P was unsuccessful.[4] In turn, direct conversion of 2 to the sulfide (5), $[\alpha]_D^{30}$ -172° (EtOH), was realized by treatment with diphenyldisulfide and tri-n-butyl phosphine in pyridine at room temperature for 2 days in 83% yield.[5] Oxidation of 5 with sodium meta-periodate in aq.MeOH gave an epimeric mixture of sulfoxides (6)(86%), desired nucleophilic partner for carbon-carbon coupling. The construction of the whole carbon skeleton of 1 was achieved by coupling of the sulfoxide (6) with trans allylic bromide (7)[6] derived from trans-10-hydroxygeranyl benzyl ether.[7] Thus, the sulfoxide (6) was lithiated with an equivalent of lithium diisopropylamide in THF at -20° under argon for 30 min. A THF solution of the bromide (7) was added into the solution of the lithiated sulfoxide and the mixture was gradually warmed up to 10° (during ca. 1 hr). A usual work-up afforded a diastereoisomeric mixture of coupled sulfoxides (8). After rough chromatographic removal of a trace amount of the remaining bromide (7) on silica gel, the crude sulfoxide (8) was submitted to the Birch reduction with lithium in ethylamine at -78° for 30 min followed by quenching with 1,3-butadiene. Purification of the resulted crude alcohol by columun chromatography on silica gel gave oily 1 (60% overall yield from the sulfoxde (6)), $[\alpha]_D^{30}$ -96°(MeOH), which was identified with authentic natural caulerpol (1)[1] provided by Dr. A. J. Blackman, in every respect involving optical rotation. Thus, the absolute configuration of the asymmetric center (*) of 1 was determined as (S).

The successful use of optically active α-cyclogeraniol (2) described above appears to be promising for its application to syntheses of terpenes possessing the partial structure (A) in the molecules, e.g., pallescensin-1, -A, and ferruginol.

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References and Notes

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3) a) M. Shibasaki, S. Terashima and S. Yamada, Chem. Pharm. Bull., 23, 272, 279 (1975) and references cited therein; b) T. Matsumoto and S. Usui, Chem. Lett., 1978, 105, 897.

4) Bromination of γ-cyclogeraniol under analogous conditions was also unsuccessful; unpublished results.

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6) The bromide (7) was obtained from the corresponding alcohol by treatment with PBr$_3$ in ether at 0° for 20 hr in 85% yield.

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