Tetrahedron Letters No. 11, pp 945 - 948, 1978. Pergamon Press. Printed in Great Britain.

PARTIAL RESOLUTION OF GERMACRONE. AN OPTICALLY ACTIVE DISSYMMETRIC TRANS, TRANS-1,5-CYCLODECADIENE.

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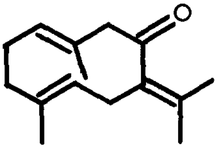
(Received in USA 26 January 1977; received in UK for publication 23 January 1978)

The possibility that, despite the lack of an asymmetric center, trans-cycloalkenes of medium ring size might be capable of existing in stable enantiomeric forms was suggested some years ago [3] and quickly verified by Cope's imaginative resolution of trans-cyclooctene [4], cis,trans-1,5-cyclooctadiene [5], and trans-cyclononene [6]. The latter racemizes rapidly at 0° C, however, and trans-cyclodecene could not be resolved at all [6]. It has been calculated [7] from variable temperature nmr studies that the barrier to rotation of the double bond through the saturated loop of trans-cyclodecene is so low that the optical half-life of one enantiomer at 25° C would be 10^{-4} seconds.

There is recurring and persuasive evidence [8], however, particularly among the germacrane family of sesquiterpenes [9], that a second trans double bond at the 5,6-position of trans-cyclodecene raises the conformational inversion barrier substantially, suggesting that in some of these systems stable enantiomers might be isolable (Figure 1). We have sought to realize this possibility by resolving a germacrane derivative devoid of asymmetric centers, and report here our preliminary success in achieving partial resolution of the sesquiterpene ketone, germacrone (1) [10].

Figure 1. Enantiomeric trans,trans-1,5-cyclodecadienes.

Germacrone, as isolated from Zdravets oil, is optically inactive [11]. Conventional attempts at resolution were unsuccessful, since the acid phthalate of germacrol (2) did not form crystalline salts with a number of alkaloids, and fermenting yeast [12] did not reduce germacrone to alcohol (2). Reduction of germacrone with the $LiAlH_4$-quinine reagent [13], however, afforded germacrol (a mixture of diastereomers, with both the asymmetric carbon and dissymmetric ring system as elements of asymmetry) with optical rotations ranging from $+ 9.9^0$ to $+ 29^0$ ($CHCl_3$) in several runs. Incomplete oxidation with CrO_3 in aqueous pyridine, taking advantage of different rates of oxidation of the diastereomers of (2), returned crystalline germacrone with rotations of $[\alpha]_D^{30} - 0.038^0$ (c 21.2, $CHCl_3$) to $[\alpha]_D^{25} - 1.4^0$ (c 1.3, cyclohexane) in several experiments.



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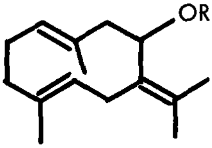
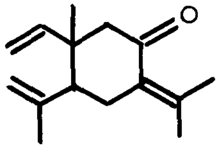


2 R=H

3 R= $-CONHCH(CH_3)Ph$

4 R= $-COCH_2O$-(l-menthyl)



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Higher rotations were achieved by kinetic resolution of (2) (the optically active mixture from $LiAlH_4$-quinine reduction) with (+)-α-phenylethylisocyanate. The sluggish reaction was allowed to proceed for eight days at room temperature, when TLC showed reaction to be roughly 50 % complete, and the urethan (3), $[\alpha]_D^{26} + 58^0$ (c 5.7, EtOH), was separated from unreacted alcohol by preparative TLC. Reduction of the urethan with "Red-Al" gave germacrol, $[\alpha]_D^{33} + 13.7^0$ (c 5.13, EtOH), which was then oxidized with Collins' reagent to germacrone, which showed $[\alpha]_D^{25} - 2^0$. The unreacted germacrol, $[\alpha]_D^{33} + 31.2^0$ (c 4.32, EtOH), was separately oxidized to germacrone. Recrystallization from aqueous ethanol gave a first crop of needles, mp 56^0, $[\alpha]_D^{28} - 0.68^0$ (c 12, EtOH), while from the mother liquors a second crop of crystalline germacrone was obtained with $[\alpha]_D^{33} - 42.5^0$ (c 9.07, EtOH), $[\alpha]_{400}^{25} - 210^0$ (c 0.28, EtOH). This is apparently one of the cases in which the racemate is less soluble than either enantiomer, so that the mother liquors are enriched in the optically active form by recrystallization.

An alternate method of partial resolution was separation of the mixture of diastereomeric l-menthoxyacetates (4), $[\alpha]_D^{22} - 46^0$ (c 4.3, $CHCl_3$), derived from racemic (2), using gradient elution chromatography on Merck silica gel G, beginning with hexane and ending with 1:1 hexane-benzene. The first fractions of (4), $[\alpha]_D^{25} - 112^0$ (c 6.2, $CHCl_3$), were reduced with $LiAlH_4$ to germacrol of $[\alpha]_D^{25} - 59^0$ (c 2.5, $CHCl_3$), which then afforded germacrone , mp 52-53^0, $[\alpha]_{470}^{25} + 30^0$ (c 0.45, dioxan) on oxidation with Sarett reagent. The final fractions of menthoxyacetate, $[\alpha]_D^{25} - 20^0$ (c 3.5, $CHCl_3$), subjected to the same sequence of reduction and oxidation, gave germacrone, mp 53-54^0, $[\alpha]_D^{24} - 2.67^0$ (c 1.8, $CHCl_3$).

While these initial experiments have not yielded germacrone of high optical purity, the obtention of pure recrystallized samples with appreciable optical rotation, both dextro- and levorotatory, from several different experimental approaches, demonstrates unambiguously that the molecule is dissymmetric. Solid samples have been kept for months at room temperature without loss of optical activity, in contrast to the report[14] that inversion of the ten-membered ring is rapid on the NMR time scale at room temperature. A referee has suggested that the rotations of the ring double bonds may be rapid and that the dissymmetry resides instead in the twisted isopropylidene moiety. There is no doubt that this element contributes appreciably to the barrier to enantiomer interconversion, and it seems likely that both factors are necessary for the observed optical stability[15].

The ORD and CD spectra of (-) germacrone reveal a negative Cotton effect at about 310 nm, but in the absence of suitable models there does not seem to be any way to relate this to the absolute configuration. The work of Takeda [18], Wharton[19], and others has shown that the Cope rearrangement of 1,5-cyclodecadienes is stereospecific, in that the configuration of the rearrangement product is a function of the diene conformation. If optically active germacrone could be rearranged to pyrogermacrone (5) at temperatures below those causing racemization, the absolute configuration of the product [20] could be used to deduce the absolute configuration of the chiral ring system in germacrone. Unfortunately, our experiments have so far not given clearcut results. In four runs, pyrolysis of optically active germacrone at 115-125^0 for 1-7 days has afforded optically active products, but the difficulty of cleanly separating (5) from unrearranged (1) on this scale, along with the low optical rotations, has made it difficult to determine with certainty whether the pyrogermacrone is optically active.

Acknowledgments. This work was supported by research grant GP-28056 from the National Science Foundation, to whom the authors express their appreciation. We thank Dr. Alan F. Thomas, Firmenich et Cie, for a generous sample of germacrone, and Mr. Martin Stewart for measurement of optical rotations.

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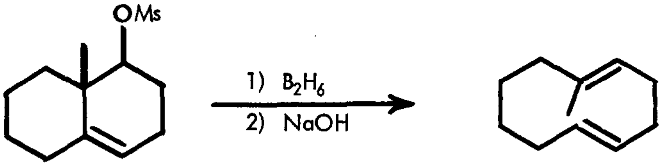

(**6**) (**7**)

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