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TRANSFORMATION OF THE DITERPENE A/B RING JUNCTURE TO THE ANTIPODAL SYSTEM. THE SYNTHESIS OF (-)-PODOCARPIC ACID FROM (+)-DEHYDROABIETIC ACID.

S. W. Pelletier, Y. Ichinohe and D. L. Herald, Jr.

Department of Chemistry, University of Georgia, Athens, Georgia 30601

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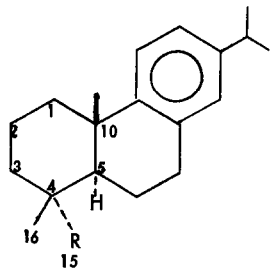
This paper describes a simple two-step sequence involving the catalytic inversion of the steroidal-type A/B ring juncture to an antipodal A/B ring juncture. This procedure has been employed in the synthesis of (-)-podocarpic acid (enantiopodocarpic acid) from (+)-dehydroabietic acid.

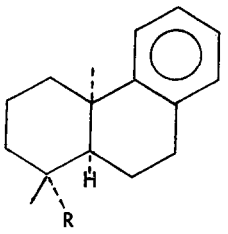
Skeletons having the nonsteroidal (antipodal) configuration at the A/B ring juncture have been reported for many naturally occurring diterpenoids and some sesquiterpenoids. Many of these compounds, particularly the diterpene alkaloids, penta-, tetra-, and bi-cyclic diterpenes have notable, physiological activity. The overall synthesis of such active compounds would be greatly simplified if the antipodal A/B ring juncture could be introduced in a few simple steps from the structurally related and more readily available, optically active starting materials having the steroidal-type A/B ring juncture.

The isomerization of angular methyl groups in certain natural steroids and related terpenes from the β- to the α-configuration is well known. Such reaction have been accomplished via the u.v.-irradiation of photosensitive compounds capable of an $n \longrightarrow \pi^*$ transition (e.g. ergosterol[1], santonin[2], and androsterone[3a]). Other compounds (e.g. 9-methyldecaline[4] and dehydroabietonitrile[5a]) have been reported to undergo angular methyl reorientation when treated with $AlCl_3$ under Friedel-Crafts reaction conditions.

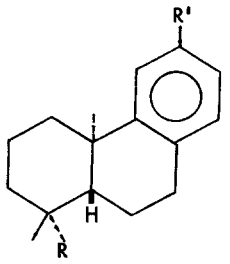
We wish to report herein a simple, convenient method for the inversion of the steroidal-type A/B ring juncture to the antipodal one by the use of two catalytic reactions. The first reaction is exemplified by the behavior of two A/B trans compounds of the abietic type (I and II). These diterpenes are readily isomerized by a reverse Friedel-Crafts reaction[6a,b] to the A/B cis compounds upon treatment with aluminum chloride in dry benzene (accomplished with the loss of the isopropyl group). Both products (III and IV) have the A/B cis ring juncture with the C(10)-angular methyl group in the α-orientation[5,6b]).



I, $R=CO_2H$
II, $R=CN$



III, $R=CO_2H$
IV, $R=CN$
V, $R=CO_2CH_3$



VI, $R=CN$; $R'=H$
VII, $R=CO_2CH_3$; $R'=H$
VIII, $R=CO_2CH_3$; $R'=COCH_3$
IX, $R=CO_2CH_3$; $R'=OH$

We have found that the subsequent isomerization of 5α, 10α -podocarpa-8,11,13-trien-15-nitrile (IV) to 5β, 10α-podocarpa-8,11,13-trien-15-nitrile (VI)[5a], m.p. 87-88°; i.r. (KBr): 2225 cm^{-1} (C≡N); n.m.r. ($CDCl_3$): τ = 1.57 (3H, s, C(4)-CH_3), 1.23 (3H, s, C(10)-CH_3) can be easily accomplished via treatment with 10% palladium-charcoal catalyst[7a,b] in refluxing triglyme for 3 hours. Optimum yields (85%) were afforded when the product was purified by sublimation. Analogously, the isomerization of methyl 5α, 10α-podocarpa-8,11,13-trien-15-oate (V) afforded in a yield of 83% methyl 5β,10α-podocarpa-8,11,13-trien-15-oate (VII)[8a], m.p. 139.5-141.5°; i.r. (KBr): 1727 cm^{-1} ($COOCH_3$); n.m.r. ($CDCl_3$): τ = 6.33 (3H, s, $COOCH_3$), 8.73 (3H, s, C(4)-CH_3), 8.97 (3H, s, C(10)-CH_3). Although the antipodal compounds VI and VII have been previously synthesized[5a,8a] via alternate routes from IV and V respectively, much poorer yields (ca. 4% and 20% respectively) were obtained. Thus, the combination of the reverse Friedel-Crafts reaction and the much improved, palladium isomerization provides a convenient and economical procedure for the conversion of natural diterpenes to their antipodal A/B ring system isomers.

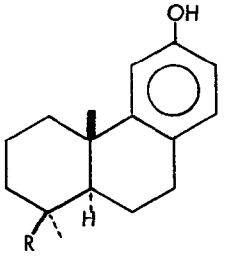
The antipodal compound VII proved to be an important intermediate in the total synthesis of antipodal diterpenes, the synthetic value of VII being demonstrated by the preparation of (-)-podocarpic acid, as described below.

Friedel-Crafts acetylation of VII with acetyl chloride in carbon disulfide for one hour[5b] resulted in the formation of (-)-methyl 12-acetyldeoxypodocarpate (VIII, methyl 12-acetyl-5β,10α-podocarpa-8,11,13-trien-15-oate), m.p. 158-160°; $[\alpha]_D^{22}$ -153.5° (c, 0.55, abs. EtOH); i.r. (KBr): 1681 cm^{-1} (-$COCH_3$), 1708 cm^{-1} (-$COOCH_3$); n.m.r. ($CDCl_3$): τ = 6.28 (3H, s, -$COOCH_3$), 7.41 (3H, s, Ar-$COCH_3$), 8.69 (3H, s, C(4)-CH_3), 8.92 (3H, s, C(10)-CH_3) in a 43% yield (based on consumed starting material).

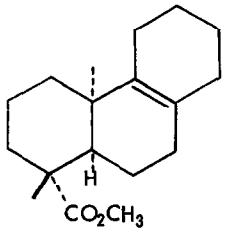
Baeyer-Villiger oxidation of VIII with hydrogen peroxide in the presence of catalytic amounts of selenium dioxide in refluxing tertiary butyl alcohol[9] gave directly (-)-methyl podocarpate (IX), m.p. 211-212°; i.r. (KBr): 3420 cm^{-1} (-OH), 1690 cm^{-1} (-$COOCH_3$); n.m.r. ($CDCl_3$): τ = 6.17 (3H, s, -$COOCH_3$), 8.59 (3H, s, C(4)-CH_3), 8.91 (3H, s, C(10)-CH_3) in a 47% yield. No (-)-methyl 12-acetoxypodocarpate

could be detected. The infrared and n.m.r. spectra of IX and an authentic sample of (+)-methyl podocarpate (X), obtained by methylation of natural (+)-podocarpic acid (XI), were identical. Additional proof of the enantiomeric relationships between IX and X was afforded by the fact the two compounds had nearly identical absolute rotation values, but of opposite signs ($[\alpha]_D^{22}$ for IX = -102.8°; and $[\alpha]_D^{22}$ for X= +104.4°).

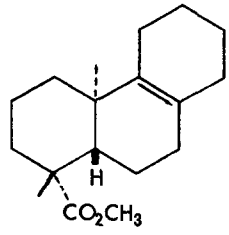
Further evidence indicating the usefullness of the improved palladium isomerization reaction was demonstrated by the conversion of methyl 5α, 10α-podocarpa-8(9)-en-15-oate (XII) (obtained from a modified Birch reduction ($Li/CH_2NH_2)_2$)[10] of 5α,10α-podocarpa-8,11,13-trien-15-oic acid (III) and subsequent methylation) with CH_2N_2 to methyl 5β,10α-podocarpa-8(9)-en-15-oate (XIII)[8b], m.p. 83-86°; i.r. (KBr): 1720 cm^{-1} ($COOCH_3$); n.m.r. ($CDCl_3$): τ = 6.41 (3H, s, $COOC\underline{H}_3$), 8.84 (3H, s, C(4)-$C\underline{H}_3$), 9.26 (3H, s, C(10)-$C\underline{H}_3$) in a yield of 67%.



X, $R=CO_2CH_3$
XI, $R=CO_2H$



XII



XIII

Attempts to isomerize steroidal derivatives (e.g. methyl 3,7-diacetylcholate and methyl dehydrocholate), containing saturated skeletons, with Pd-C were less successful[11]. Interestingly, the treatment of estrone (XIV) with Pd-C catalyst in refluxing triglyme provided moderate yields (48%) of (+)-isoequilenin (XV) having the C/D cis ring juncture; assigned as the acetate, m.p. 154-156°; i.r. (KBr): 1770 cm^{-1} ($-OCOCH_3$), 1745 cm^{-1} (5 membered C=O); n.m.r. ($CDCl_3$): τ = 1.83-2.75 (5H, m, aromatic), 6.86 (2H, t, C(16)-$C\underline{H}_2$-), 7.65 (3H, s, $OCOC\underline{H}_3$), 8.86 (3H, s, C(18)-$C\underline{H}_3$). A similar isomerization of XIV has been previously mentioned by Butenandt et al[3b].

A radical mechanism may be involved in the preceeding palladium catalyzed reactions. Presumably, the hydrogen abstracting character of palladium facilitates the conversion of the ring juncture to the thermodynamically more stable form.

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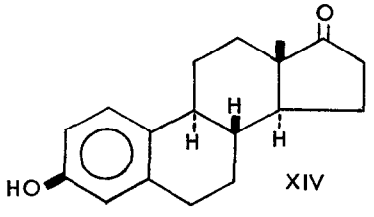
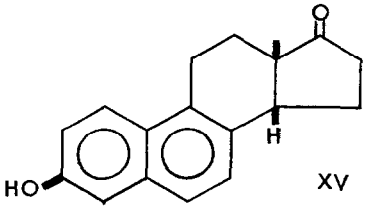


XIV



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