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SYNTHESIS OF A CHIRAL 1,1,3-TRIMETHYLCYCLOHEXANE DERIVATIVE FROM d-CAMPHOR: A POTENT KEY BUILDING BLOCK FOR ENT-TAXANE-TYPE DITERPENOIDS

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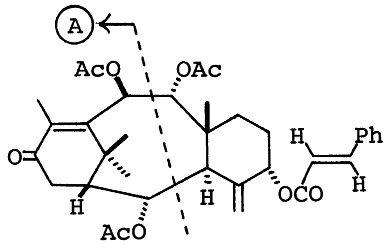
A chiarl 1,1,3-trimethylcyclohexane derivative (12), which is a potent key building block for synthesis of *ent*-taxane-type diterpenoids, has been prepared from d-camphor (2) through a conversion pathway which involves a novel ring enlargement reaction of a 1,1,2-trimethylcyclopentane derivative (3).

During the course of our synthetic studies on taxane-type diterpenoids1) [*e.g.* taxinine (1)2)], we have required a chiral 1,1,3-trimethylcyclohexane derivative (12) which possesses functionarized methyl groups at C-2 and C-6. We wish to report herein a synthetic pathway starting from d-camphor (2) leading to the desired allyl alcohol (12) which formally constitutes an antipodal building block for the segment A in the target skeleton (1). The synthetic pathway involves a novel ring enlargement (*cf.* i) of a vinylcyclopentane derivative (3) prepared from d-camphor (2)3) to a cyclohexane derivative (4). This conversion was achieved by treatment with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO).4)

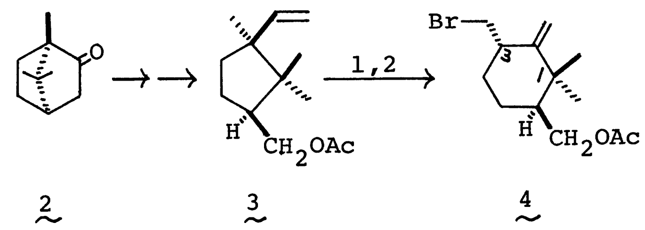
Bromination of the vinylcyclopentane (3) with 1.5 eq. of TBCO in THF under reflux gave a complex mixture which, however, was converted to a mixture of 4 (63%) and 3 (24%, recovered) on treatment with Zn-AcOH at 60°C. 4, oil, $C_{13}H_{21}O_2Br$,5) $[\alpha]_D$ +62°($CHCl_3$). IR (film) cm^{-1}: 3080, 1633, 900 (terminal methylene); 1750, 1240 (acetate). ^1H-NMR (CCl_4) δ: 1.10, 1.22, 2.00 (3H each, all s, tert-CH_3 x 2, OAc); 3.2-3.8 (2H, AB in ABX, $-\overset{|}{C}H-C\underline{H}_2-Br$); 3.8-4.2 (2H, AB in ABX, $-\overset{|}{C}H-C\underline{H}_2-OAc$); 4.58, 4.86 (1H each, both br.s, $>C=C\underline{H}_2$).

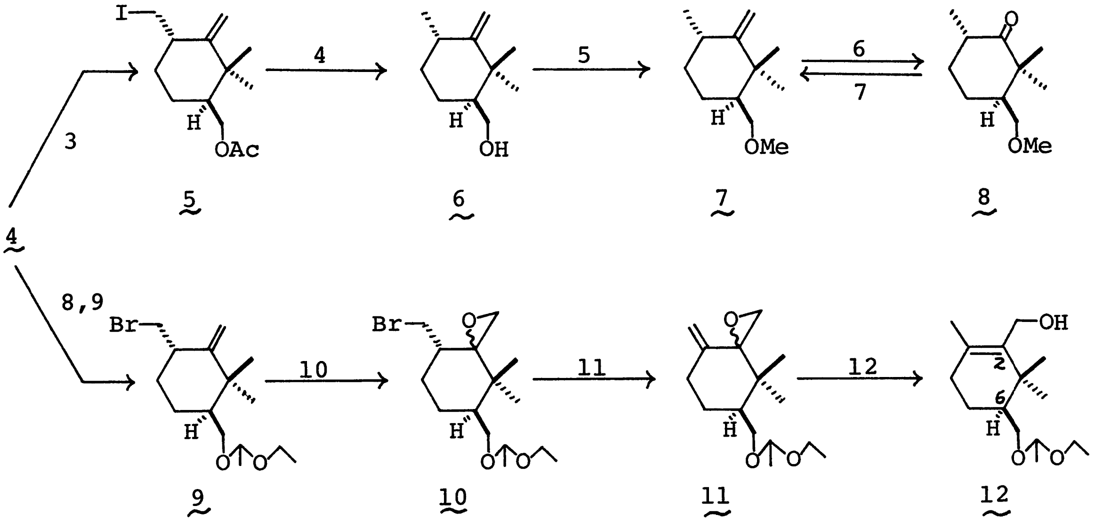
The structure of 4 including the C-3 configuration was substantiated on the basis of following experiments. Treatment of 4 with NaI in acetone under reflux gave quantitatively an iodo acetate (5), oil, $C_{13}H_{21}O_2I$, $[\alpha]_D$ +33°$(CHCl_3)$. IR (film): 3080, 1740, 1623, 900. δ (CCl_4): 0.99, 1.20, 1.95 (3H each, all s); 3.0-3.5 (2H, AB in ABX); 3.8-4.2 (2H, AB in ABX); 4.63, 4.88 (1H each, both br.s). Reduction of 5 with $LiAlH_4$ in THF at room temp. furnished quantitatively an alcohol (6), oil, $C_{11}H_{20}O$, $[\alpha]_D$ +100°$(CHCl_3)$. IR (film): 3400, 3095, 1633, 892. δ (CCl_4): 0.94, 1.19 (3H each, both s); 1.03 (3H, d, J= 6, sec-CH_3); 3.2-3.8 (2H, AB in ABX, $-\overset{|}{C}H-C\underline{H}_2OH$); 4.59, 4.73 (1H each, both br.s). Methylation of 6 with NaH-DME-MeI afforded in 92% yield the methyl ether (7), oil, $C_{12}H_{22}O$, $[\alpha]_D$ +99°$(CHCl_3)$. IR (film): 3085, 1622, 897. δ (CCl_4): 0.93, 1.15, 3.22 (3H each, all s, tert-CH_3 x 2, OMe); 1.02 (3H, d, J= 6); 3.0-3.5 (2H, AB in ABX, $-\overset{|}{C}H-C\underline{H}_2OMe$); 4.58, 4.72 (1H each, both br.s). Ozonolysis of 7 in MeOH at -72°C yielded in 65% yield a cyclohexanone derivative (8), oil, $C_{11}H_{20}O_2$, $[\alpha]_D$ +129°$(CHCl_3)$. IR (film): 1700. δ (CCl_4): 1.00, 1.07, 3.24 (3H each, all s); 0.93 (3H, d, J= 6); 2.55 (1H, m, $-CO-\overset{|}{C}\underline{H}-CH_3$); 3.1-3.5 (2H, AB in ABX). In the spin decoupling experiments of 8, a multiplet at δ2.55 assignable to 3-H changed to a doublet of doublets (J=10,6 Hz) upon irradiation at δ0.93 (3-CH_3). In addition, a positive maximum ($[\phi]_{294}$+4900) was observed in the CD spectrum of 8, thus supporting its 3α-CH_3 configuration. Furthermore, the Wittig methylenation of 8 with methyltriphenylphosphonium bromide and t-AmONa[6] yielded in 74% yield a product which was identical with the parent methyl ether (7) in all respects. It has become evident that the C-3 configuration of 7 was preserved during the ozonolysis.

Alkali hydrolysis followed by treatment with ethyl vinyl ether and p-TsOH·H_2O of the starting bromo cyclohexane (4) furnished quantitatively a bromo ether (9), oil, $C_{15}H_{27}O_2Br$, $[\alpha]_D$ +60°$(CHCl_3)$. IR (film): 3080, 1626, 890. δ (CCl_4): 0.97, 1.19 (3H each, both s); 1.14 (3H, t, J= 6, $-O-CH_2-C\underline{H}_3$); 1.26 (3H, d, J= 5, $-O-CH(C\underline{H}_3)-O-$); 3.0-3.8 (6H, m, $-\overset{|}{C}H-C\underline{H}_2-Br$, $-\overset{|}{C}H-C\underline{H}_2-O-$, $-O-C\underline{H}_2-CH_3$); 4.53 (1H, q, J= 5, $-O-C\underline{H}(CH_3)-O-$); 4.54, 4.83 (1H each, both br.s, $>C=C\underline{H}_2$). Oxidation of 9 with m-chloroperbenzoic acid in CH_2Cl_2 afforded a mixture of two epimeric epoxides (10a and 10b)[7]. 10a (50%), oil, $C_{15}H_{27}O_3Br$, $[\alpha]_D$ +10°$(CHCl_3)$. IR (film): 3045, 935. δ (CCl_4): 0.82, 1.00 (3H each, both s); 1.14 (3H, t, J= 7); 1.22 (3H, d, J= 5); 2.7-3.5 (8H, m, $-\overset{|}{C}H-C\underline{H}_2-Br$, $-\overset{|}{C}H-C\underline{H}_2-O-$, $-O-C\underline{H}_2-CH_3$, $>C\overset{O}{\frown}C\underline{H}_2$); 4.55 (1H, q, J= 5). 10b (42%), oil, $C_{15}H_{27}O_3Br$, $[\alpha]_D$ +55°$(CHCl_3)$. IR (film): 3045, 935, 883. δ (CCl_4): 0.81, 0.99 (3H each, both s); 1.14 (3H, t, J= 7); 1.22 (3H, d, J= 5); 2.4-3.8 (8H, m); 4.56 (1H, q, J= 5). Treatment of one isomer (10a) with DBU by

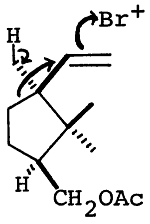


1





1) TBCO; 2) Zn-AcOH; 3) NaI; 4) $LiAlH_4$, THF; 5) NaH-DME, MeI; 6) O_3; 7) ϕ_3PCH_3Br, t-AmONa; 8) KOH-MeOH; 9) ⁄⁄⁀O⁀, p-$TsOH{\cdot}H_2O$; 10) m-CPBA, CH_2Cl_2; 11) DBU; 12) Na, NH_3.



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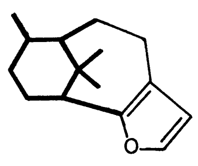
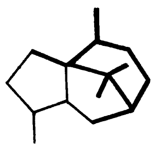


ii
(cf. pallescensin C)



iii
(cf. cyperene)

heating at 110°C gave an α,β-unsaturated epoxide (11a) whereas the similar treatment of another isomer (10b) gave another epoxide (11b).7) In practice, however, treatment of the mixture of bromo epoxides (10) with DBU afforded in good yield a mixture of α,β-unsaturated epoxides (11) which, without further purification, was converted on treatment with sodium in liquid ammonia in 79% yield to the final allyl alcohol (12), oil, $C_{15}H_{28}O_3$, $[\alpha]_D$ -39°($CHCl_3$). IR (film): 3615, 3480, 1645. δ (CCl_4): 0.87, 1.12 (3H each, both s, tert-CH_3 x 2); 1.16 (3H, t, J= 7, $-O-CH_2-C\underline{H}_3$); 1.23 (3H, d, J= 5, $-O-CH(C\underline{H}_3)-O-$); 1.72 (3H, s, $C\underline{H}_3-\overset{|}{C}=\overset{|}{C}-$); 2.9-3.8 (4H, m, $-\overset{|}{C}H-C\underline{H}_2-O-$, $-O-C\underline{H}_2-CH_3$); 4.00 (2H, s, $-\overset{|}{C}=\overset{|}{C}-C\underline{H}_2OH$); 4.59 (1H, q, J= 5, $-O-C\underline{H}(CH_3)-O-$).

The allyl alcohol (12) seems to be a potent key building block for ent-taxane-type diterpenoids. A synthetic pathway starting from l-camphor would provide a building block for taxane-type diterpenoids. It is interestingly pointed out here that the allyl alcohol (12) also appears to be a promising starting compound for syntheses of other terpenoids (e.g. pallescensin C,8) cyperene,9); their planar carbon skeletons (ii, iii) are given).

We are currently continuing synthetic studies on taxane-type diterpenoids by employing the allyl alcohol (12) and allied compounds as the building blocks.

References and Notes

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