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TOTAL SYNTHESIS OF (±) ISOCLOVENE

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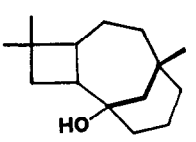
SUMMARY: A new total synthesis of the title compound, centering around an intramolecular Michael addition to set up the characteristic tricyclo-$-\left[6.2.2.0^{5,12}\right]$-dodecane system, is described.

On treatment with phosphorus pentoxide (or preferably with polyphosphoric acid) caryolan-1-ol 1 is converted to a number of rearranged sesquiterpenes, among which isoclovene 2[1].

Its structure was determined by an X-ray crystallographic analysis of the corresponding hydrochloride[2], presenting the rather unusual tricyclo-$-\left[6.2.2.0^{5,12}\right]$- dodecane system as a challenging synthetic target.

In considering a synthetic approach to this novel skeleton, we focused on creating ring C onto a preformed AB ring system. The central issue to this approach involved the design of an intramolecular Michael addition of the key intermediate 3 to build up the seven membered ring C as in 4.



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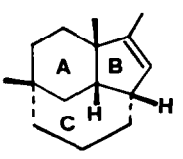

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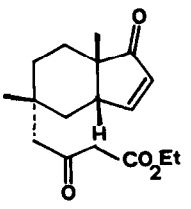

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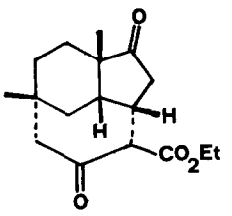

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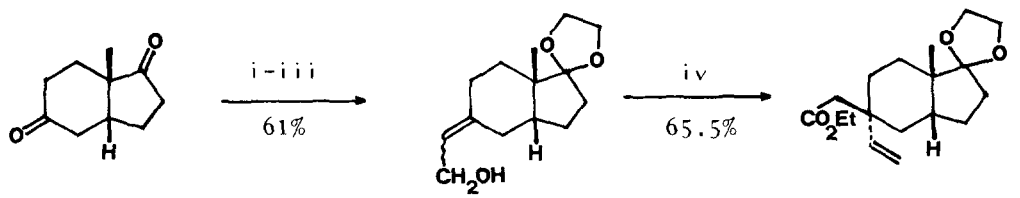
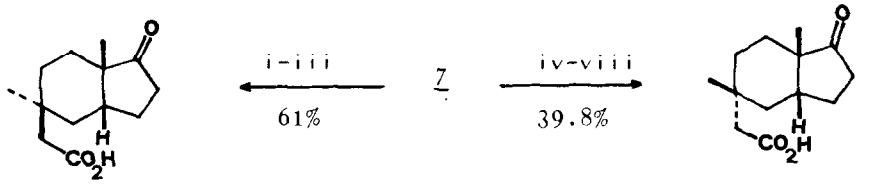
Examination of molecular models showed that this operation was very feasible provided the quaternary center at C-5 possesses the correct stereochemistry. The [3,3] sigmatropic rearrangement of the ketalized allylic alcohol 6*, obtained as 1:1 E/Z mixture in three steps from the known[3] hydrindandione 5, was ideally suited for the establishment of the desired stereochemistry at the quaternary center of 7, both the created substituents being amenable for a degradation to a methyl group.



5 6 7

Reagents: i, $(Ph)_3P{=}CH{-}CO_2Et$; ii, $(CH_2OH)_2$, H^+; iii, $LiAlH_4$; iv, $MeCH(OEt)_3$, propionic acid, 140-150°C.

Thus 7 may be converted by standard steps, alternatively to 8 (m.p. 132°C) or 9 (m.p. 112°C) only the latter being suitable for our protocol.**

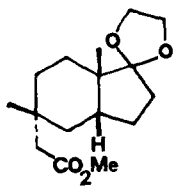


8 9

Reagents 7⟶8; i, O_3, $(Ph)_3P$; ii, $(CH_2SH)_2$, $BF_3.Et_2O$; iii, Raney-Ni
7⟶9; iv, $LiAlH_4$; v, PCC; vi, C/Pd, 200°C; vii, B_2H_6, H_2O_2, NaOH; viii, Jones.

The ketal ester 10 was converted to the αβ-unsaturated keto-acid 11 by successive bromination (pyridine hydrobromide perbromide, THF), dehydrohalogenation (DBU, xylene, reflux 8 hs.), alkaline hydrolysis (K_2CO_3, MeOH,

H_2O; reflux 5 hs.), followed by brief acid treatment to remove the protective group (51.5% overall yield).



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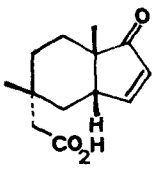

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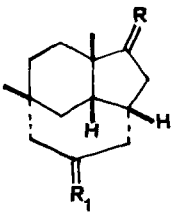
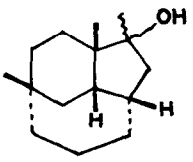


12 R=O; R_1=O

13 R=OCH_2CH_2O; R_1=O

14 R=O; R_1=H,H



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The chain extension to produce the oily synthon 3 was achieved by condensation of 11, activated as imidazolide (carbonyldiimidazole, THF, room temperature), with the magnesium salt of monoethyl malonate under essentially neutral conditions[6], followed by exposure of the crude reaction mixture to ethanolic potassium carbonate to promote intramolecular Michael addition to 4 (m.p. 77°C; 80%).*** Deethoxycarbonylation[7] (DMSO, H_2O, NaCl) of 4 afforded quantitatively 12 as a crystalline compound (m.p. 95°C), which displayed chemoselectivity towards 2-methyl-2-ethyl-1,3-dioxolane (MED) producing a 90% yield of the mono-ketal 13 (m.p. 119°-120°C). Wolff-Kishner reduction (NH_2NH_2 diethylene glycol, NaOH; 200°C) followed by acid treatment yielded the oily ketone 14[8] (62% yield), which reacted with MeMgI to produce quantitatively the tertiary alcohol 15. The latter was eventually transformed to 2 by iodine promoted dehydration (98% yield). The IR and the more significant ^1H NMR spectrum of pure synthetic 2 [δ=0.87 (s, 3H); 1.02 (s, 3H); 1.58 (dd, 3H, J=3Hz, J=2Hz) 2.8-3.12 (m, 1H), 5.12 (m, 1H)], the salient feature of which is the double doublet of the vinylic methyl group coupled to both vinylic and allylic protons, were in complete agreement with those of the natural compound.[9] A slight impurity[8] contained in the latter does not interfere in the comparison.

References and Notes

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* All new compounds were fully characterized by spectroscopic and microanalytical methods.

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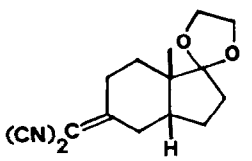
** The structural proof of both these compounds follows from X-ray crystallographic analysis. We thank Prof. G. Gilli, Istituto Chimico, Ferrara, for this determination. The "unwanted" isomer 8 was obtained as the sole product by $LiMe_2Cu$ conjugate addition to (i) followed by saponification.



(i)

The stereochemical outcome of this addition may account for earlier unsuccessful attempts to gain access to the tricyclo $[6.2.2.0^{5,12}]$ dodecane system by similar routes.[4,5]

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*** Isolation of pure 3 at this stage may be complicated by the presence of some product deriving by the addition of imidazole to the $\alpha\beta$-unsaturated ketone moiety, which suffers retro-Michael reaction on treatment with K_2CO_3 allowing the complete conversion 3 ⟶ 4 .

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