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# A Regio and Stereospecific Radical Annulation Route to Chiral Tricyclo[4.3.1.$0^{3,7}$]decane (Isotwistane) System[1] Synthesis of (+)-10-α-Naphthyl-5-epi-Pupukean-9-one

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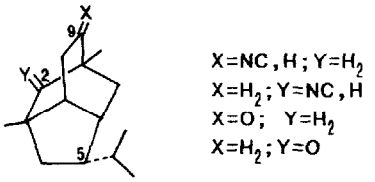
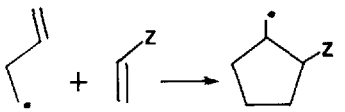
*Key words: Radical cyclisation; annulation; isotwistane; pupukeanone.*

***ABSTRACT:*** *Contrary to that of phenyl derivative 1 the radical 4 adds to radicophiles in an inter- followed by intra-molecular radical Michael addition (radical annulation), furnishing a novel route to chiral isotwistanes 5.*

The marine natural products, pupukeananes,[2] contain the unique tricyclo [4.3.1.$0^{3,7}$]decane, *isotwistane*, skeleton. Intermolecular Michael addition of homoallyl radical to radicophiles followed by 5-*exo* trig cyclisation of the resultant radical (eq.1), provides a novel route to cyclopentanes. Based on this radical annulation,[3] we have developed a regio and stereospecific route to chiral isotwistanes, and extended it to the synthesis of an analogue of pupukeanane,[4] (+)-10-α-naphthyl-5-epi-pupukean-9-one (11), starting from R(-) carvone (7), which is the subject of this communication.

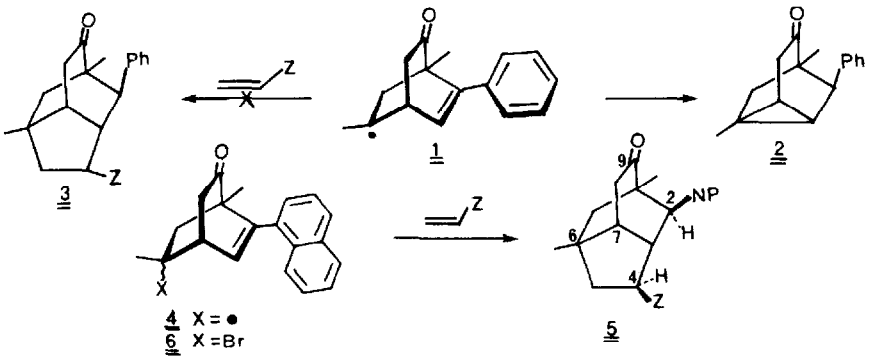


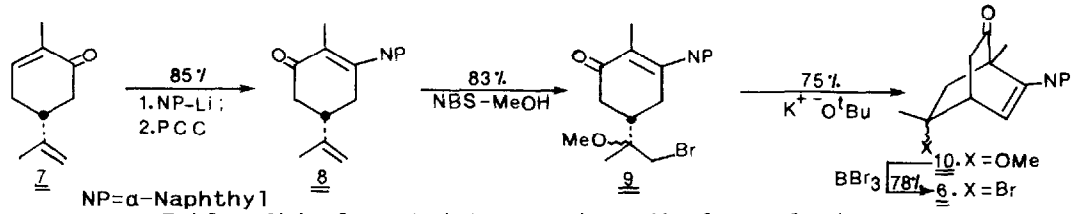

X=NC,H; Y=$H_2$
X=$H_2$; Y=NC,H
X=O; Y=$H_2$
X=$H_2$; Y=O




(eq.1)

Contrary to our expectation, generation of the radical 1 in the presence of a large excess of methyl acrylate (a radicophile) generated only the cyclopropane product 2 without any isolable amount of annulated product 3.[5] However, replacing the phenyl group in 1 with a bulky α-naphthyl group[6] changed the course of the reaction (4⟶5). This is obviously due to the lack of conjugation of the olefin moiety with the aromatic system, because of the noncoplanarity developed due to steric reasons. Thus, refluxing a 0.02 Molar






NP=α-Naphthyl

Table: Chiral Isotwistanes *via* Radical Annulation

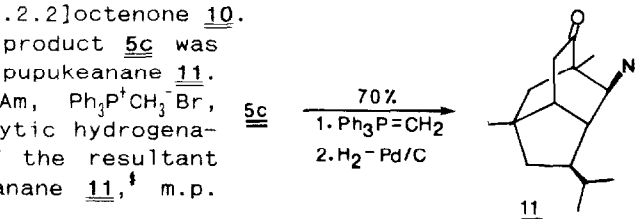
| Entry | Z | Product | Yield[a] | m.p.(°C) | $[\alpha]_D^{25}(CHCl_3)$[b] |
|---|---|---|---|---|---|
| 1 | $COOCH_3$ | 5a | 50% | 164-166 | $+96.3^0$ |
| 2 | CN | 5b | 58% | 218-220 | $+99.8^0$ |
| 3 | $COCH_3$ | 5c | 30%[c] | 196-198 | $+92.3^0$ |
| 4 | Ph | 5d | 60% | 158-160 | $+117^0$ |

(a) Refers to isolated and chromatographically pure compounds. (b) (c,1-1.5).

(c) Reaction time 2 hr with half hourly addition of extra TBTH and AIBN.

benzene solution of the bromide 6 with 1.1 eq. of tri-n-butyltin hydride (TBTH), 20 eq. of methyl acrylate and a catalytic amount of azobisisobutyronitrile (AIBN) for one hour furnished the annulated product 5a. The structure of the isotwistane 5a was clearly delineated from its spectral data.‡ The *exo, exo* stereochemistry at C-2 & C-4 was established from the weak coupling (2 & 0 Hz) of C-2 & C-4 *endo* protons with C-3 proton.[7] To test the generality of the reaction, various radicophiles were used and the results are summarised in the table. The radical precursor, bromo ketone 6 [3:2 mixture of epimers, m.p.114-16 °C, $[\alpha]_D^{25}$ +254.5° ($CHCl_3$ c,1.2)] was obtained from R-carvone (7) as depicted above, *via* the S(+)-naphthyl carvone 8, bromo methoxy enone 9 and bicyclo[2.2.2]octenone 10.

Finally, the annulated product 5c was transformed to an analogue of pupukeanane 11. Thus, Wittig reaction ($K^+{}^-O^tAm$, $Ph_3P^+CH_3{}^-Br$, $C_6H_6$) of 5c followed by catalytic hydrogenation ($H_2$-10% Pd/C, EtOAc) of the resultant olefin furnished the pupukeanane 11,‡ m.p. 120-22 °C, in 70% yield.




‡ Spectral data for 5a (Methyl 2-*exo*-4-*exo*-1,6-dimethyl-2-α-naphthyltricyclo[4.3.1.$0^{3,7}$]decan-9-one-4-carboxylate): IR($CCl_4$):1725, 1602 $cm^{-1}$. $^1H$ NMR(200 MHz,$CDCl_3$): δ 0.78(3H,s,C-1 Me), 1.21(3H,s,C-6Me), 1.69&1.84(2H,ABq,J=14.4Hz), 2.06(1H,d of ½AB,J=13.6,5.4Hz,H-5a), 2.23(1H,d of ½AB,J=13.6,9.2Hz,H-5b), 2.17(1H,m,H-3), 2.7&2.55(2H,d of ABq,J=18,3Hz,H-8), 2.72(1H,m,H-7), 3.1(1H,dd,J=9.2,5.4Hz,H-4), 3.58(1H,d,J=2.1Hz,H-2), 3.61(3H,s,COOMe), 7.08(1H,d,J=7.3Hz),7.38(1H,t,J=8Hz), 7.45-7.57(2H,m), 7.71(1H,d,J=8.2Hz), 7.86(1H, dd,J=7, 2.3Hz) & 8.08(1H,d,J=7.4Hz) (naphthyl). $^{13}C$ NMR(22.5 MHz,$CDCl_3$): δ 215.6(s,C=O), 175.9(s,O-C=O), 139.8(s), 133.8(s), 132.3(s), 129.0(d), 127.1(d), 129.3(2C,d), 123.8(d), 123.3(d), 51.6 (2C, q&d), 50.7(2C,t&d), 49.9(d), 48.0(t), 45.3(s), 43.6(d), 39.8(s), 35.5 (t), 25.7(q), 18.6(q). for 11: $[\alpha]_D^{25}$ +78° ($CHCl_3$ c,0.16). IR ($CCl_4$): 3046, 1719, 1602, 795, 777, 759 $cm^{-1}$. $^1H$ NMR(90 MHz,$CDCl_3$): δ 0.78(3H,d,J=7Hz), 0.8(3H,s), 0.84(3H,d,J=7Hz), 1.16 (3H,s), 1.1-2.05(7H,m), 2.2(1H,m), 2.6(2H,brs,H-8), 3.56(1H,brs,H-10), 7.04(1H,d,J=9Hz), 7.3-8.2(6H,m).

**REFERENCES AND NOTES**:(1) Chiral Synthons from Carvone, Part 6; for part 5 see reference 5. (2) Fusetani, N., Wolstenholme, H.J. & Matsunaga, S., *Tetrahedron Lett.*, **1990**, *31*, 5623 and references cited therein. (3) Srikrishna, A. & Hemamalini, P., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 2511 and references cited therein. (4) To our knowledge, ours is the first report on the synthesis of chiral pupukeananes. (5) Srikrishna, A., Sharma, G.V.R. & Hemamalini, P., *J. Chem. Soc., Chem. Commun.*, **1990**, 1681. (6) The presence of a radical stabilising group, e.g. aryl, at C-6 is required to control the regiospecificity of the cyclisation and also to suppress intermolecular addition of the resultant radical to one more molecule of radicophile. (7) Greuter, H. & Schmid, H., *Helv. Chim. Acta*, **1972**, *55*, 2382.

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