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Enantiospecific Construction of the Carbon Skeleton Associated with Manicol, an Antineoplastic Sesquiterpene from *Dulacia guianensis* (Olacaceae)

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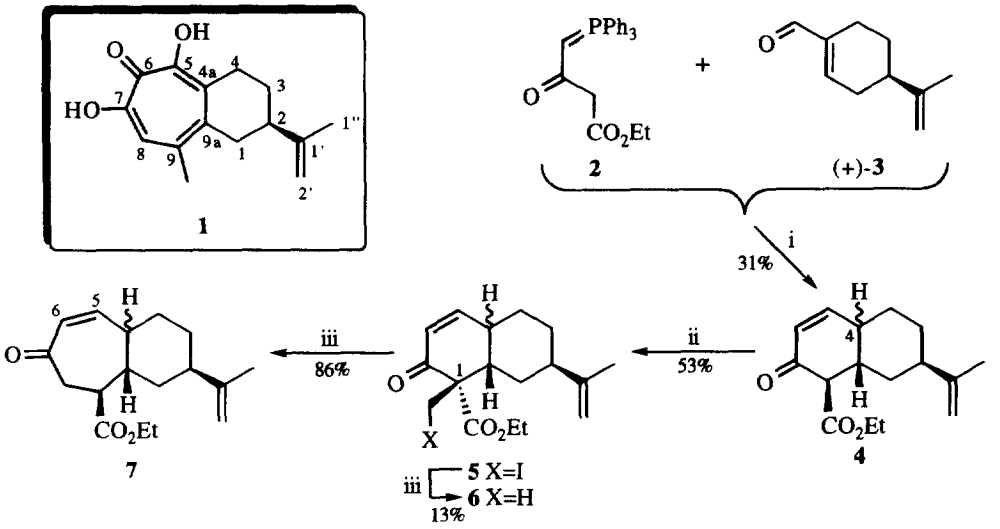
Abstract: Reaction of (*R*)-perillaldehyde [(+)-**3**] with ylid **2** provided the annulated cyclohexenone **4** which was subjected to a Beckwith-Dowd ring-expansion sequence thereby affording cycloheptenone **7**. Compound **7** embodies the full carbon skeleton associated with the sesquiterpene manicol (**1**) and possesses functionality such that it should be capable of elaboration to the natural product.

In 1980 Polonsky and co-workers reported[1] the isolation of the sesquiterpene manicol from the root bark of the Guyanan tree *Dulacia guianensis* (Olacaceae). On the basis of various spectroscopic data an eudesmane-type structure was originally assigned to the natural product. However, subsequent degradative and derivatisation studies[2] were inconsistent with this assignment thus prompting a single-crystal X-ray analysis of manicol itself. As a result the interesting troponoid structure **1** was revealed and the *R*-configuration at C-2 was determined by chemical correlation studies. Preliminary testing of manicol established that it was moderately active, *in vivo*, against P-388 lymphocytic leukaemia at non-toxic dosages of 14 mg/kg/day. However, no further examination of the biological properties of this structurally novel compound appears to have been undertaken.

From a synthetic point-of-view manicol represents a challenging target because of the lack of methodologies for the regiocontrolled construction of densely substituted troponoid nuclei and, more especially, carbannulated troponoid nuclei.[3] Of course, a further demanding feature associated with manicol is the presence of a stereogenic centre at C-2. To date, no relevant synthetic studies have been described. We now report a concise and simple method for the enantiospecific construction of the full carbon skeleton associated with manicol. The protocol described here represents a potentially useful means for (i) the cycloheptannulation of α,β-unsaturated aldehydes and (ii) the preparation of highly substituted seven-membered carbocycles.

We envisaged that the isopropenyl-substituted six-membered ring associated with manicol could be derived from (*R*)-(+)-perillaldehyde [(+)-**3**].[4] This has proven to be the case. Thus, in the first of two key steps of the reaction sequence (Scheme 1), (+)-perillaldehyde was reacted with ylid **2**[5] under conditions developed by Pietrusiewicz *et al*[6] and gave the decalin **4** {$[\alpha_D]_{21°C}$ +88.9 (*c*. 0.7 in $CHCl_3$)}, as a 5:1 mixture of diastereoisomers at C-4, in 31% yield. Treatment of compound **4** with a combination of potassium hydride and methylene iodide then provided the iodomethylated product **5** {53%, $[\alpha_D]_{17°C}$ -15.8 (*c*. 1.2 in $CHCl_3$)} as a 5:1 mixture of diastereoisomers at C-4.[7] Beckwith-Dowd ring-expansion[8] of compound **5** was effected using tri-*n*-butyltinhydride in refluxing toluene and with AIBN as initiator. Under such conditions the cycloheptenone **7**[7,9] {$[\alpha_D]_{16°C}$ +13.7 (*c*. 0.9 in $CHCl_3$)} was obtained in 86% yield and, again, as a 5:1 mixture of diastereoisomers. This ring-expanded material was accompanied by small amounts (13%) of the direct reduction product **6**.

In the 400 MHz ^{1}H NMR spectrum of compound **7** the resonances due to H5 and H6 appeared at δ 6.43 (dd, *J* =12.1 and 5.6 Hz) and δ 6.00 (dt, *J* =12.1 and 1.6Hz), respectively. The difference in chemical shift (Δ 0.43) between these two resonances is significantly smaller than the difference (Δ 0.73) between the analogous resonances in the NMR spectrum of precursor **5** and this comparison is taken as strong evidence that ring-expansion has occurred during the conversion **5** → **7**.[10]



Scheme 1: *Reagents and conditions*; (i) NaH (2 mole equiv.), trace H_2O, THF, 35°C, 20h; (ii) KH (4 mole equiv.), CH_2I_2 (4 mole equiv.), THF, 66°C, 3h; (iii) Bu_3SnH (1.2 mole equiv.), AIBN (trace), toluene, 111°C, 23h.

Compound **7** embodies the full carbon skeleton of manicol and seems suitably functionalised for elaboration to the natural product itself. Work aimed at effecting such a conversion is currently underway and results will be reported in due course.

REFERENCES AND NOTES

1. Polonsky, J., Varon, Z., Jacquemin, H., Donnelly, D. M. X. and Meegan, M. J., *J. Chem. Soc., Perkin Trans 1*, **1980**, 2065.
2. Polonsky, J., Beloeil, J-C., Prange, T., Pascard, C., Jacquemin, H., Donnelly, D. M. X. and Kenny, P. T., *Tetrahedron*, **1983**, *39*, 2647.
3. Banwell, M.G., *Aust. J. Chem.*, **1991**, *44*, 1 and references cited there-in.
4. Tius, M. A. and Kerr, M. A., *Synth. Commun.*, **1988**, *18*, 1905.
5. Serratosa, F. and Sole, E., *Anales Real Soc. Espan. Fis. Quim. (Madrid), Ser. B*, **1966**, *62(4-5)*, 431 (*Chem. Abstr.*, **1967**, *66*, 2623f).
6. Pietrusiewicz, K. M., Monkiewicz, J. and Bodalski, R., *J. Org. Chem.*, **1983**, *48*, 788.
7. The illustrated stereochemical assignments at C-1 in compound **5** and C-9 in compound **7** must be considered as tentative at this stage.
8. (a) Beckwith, A. L. J., O'Shea, D. M. and Westwood, S. W., *J. Am. Chem. Soc.*, **1988**, *110*, 2565; (b) Dowd, P. and Choi, S.-C., *Tetrahedron*, **1989**, *45*, 77.
9. Selected spectral data for compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$, 22°C) δ (major diastereoisomer) 6.43 (dd, *J* 12.1 and 5.6Hz, 1H, H5), 6.00 (dt, *J* 12.1 and 1.6Hz, 1H, H6), 4.83 (m, 1H, H2'), 4.76 (m, 1H, H2'), 4.17 (complex m, 2H, OCH_2CH_3), 2.89-2.70 (complex m, 2H), 2.67 (tm, *J* 10.4Hz, 1H), 2.47 (m, 1H), 2.27 (m, 1H), 1.85 (m, 1H), 1.70 (t, *J* 0.6Hz, 3H, H1"), 1.67-1.38 (complex m, 3H), 1.35-1.21 (complex m, 3H), 1.27 (t, *J* 7.0Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 22°C) δ(major diastereoisomer) 201.1, 174.4, 149.0, 147.3, 130.8, 110.2, 60.9, 45.4, 42.6, 38.6, 38.4, 34.0, 27.1, 22.5, 21.6, 20.8, 14.2; IR (NaCl) ν_{max} 1728 and 1665 cm^{-1}; MS (EI, 70eV) *m/z* 276 (17% of base peak) $M^{+\cdot}$.
10. Jackman, L. M. and Sternhell, S., *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd Edition; Pergamon Press: Oxford, 1969, pp. 188-192.

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