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SYNTHETIC STUDIES ON ARENE-OLEFIN CYCLOADDITIONS - V.[1] TOTAL SYNTHESIS OF (±)-ISOIRIDOMYRMECIN.

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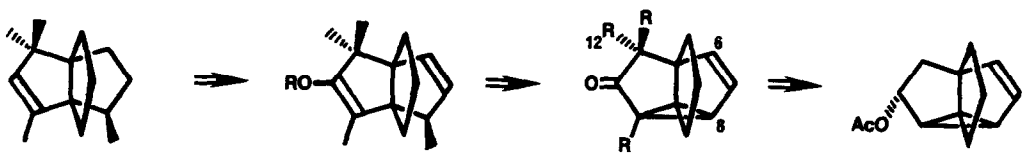
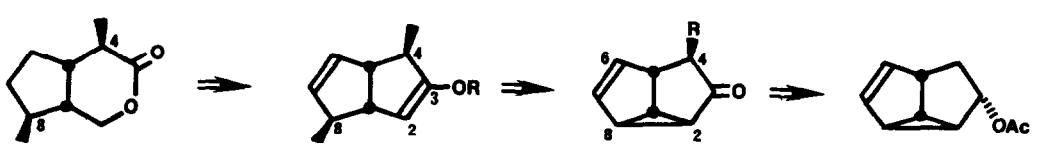
Abstract: An eight step synthesis of the iridoid isoiridomyrmecin is described, in which new methodology for the stereocontrolled elaboration of arene-olefin cycloadducts is delineated.

The arene-olefin cycloaddition[1,2] provides a general approach to polyquinane synthesis in which a tricyclo[3.3.0.0^{2,8}]octene derivative is efficiently assembled in one step with the development of up to six stereocenters. Recently, we described the use of this process for the preparation of the indan - vinyl acetate cycloadduct **5**, from which (±)-modhephene[1d] (**1**) was synthesized via the intermediates **4**, **3**, and **2**. This design served to establish the basis for analogous direct routes to other classes of five-membered ring compounds including iridoid monoterpenes[3] and the pharmacologically important carbaprostacyclins. The extension of this methodology to the problem of iridoid synthesis is described herein in a total synthesis of the ant defensive secretion, isoiridomyrmecin (**6**)[4].



1 **2** **3**: R = CH_3; **4**: R = H **5**

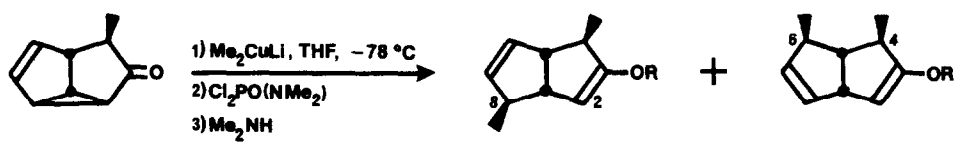


6 **7** **8**: R = CH_3; **9**: R = H **10**

For the present study, the characteristic cyclopentan-(c)-pyran iridoid ring system was expected to be derived by ozonolysis of the C2, C3 double bond of an appropriately functionalized bicyclo-octene precursor (e.g., derivable from **7**), as has been demonstrated in several laboratories[4c,d, 5]. This precursor (**7**) could in turn arise from 1,5-homoconjugate addition of $LiMe_2Cu$ to ketone **8**, if the results obtained in the modhephene synthesis (involving the conversion **3** → **2**) could be extended to the current system[6]. Finally, the formation of ketone **8** from the known[7] benzene - vinyl acetate cycloadduct **10** was anticipated to involve a sequence not unlike that (**5** → **4** → **3**) developed for modhephene, with one significant variation: while **4** had been shown to produce **3** under conditions which promote polyalkylation[1d], the present synthesis of **8** would require the stereoselective, kinetic monomethylation of semibullvalene-3-oxide (the enolate of **9**)[1d].

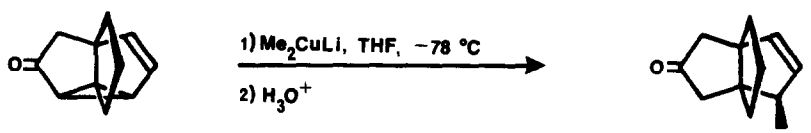
In practice, the synthesis of **8** proved to be straightforward. Photolysis of benzene and vinyl acetate[7] (Vycor, 24 hr) produced a low yield of **10** as the main isolable product, which was purified by chromatography. Deprotection of **10** ($LiAlH_4$; 89%) and oxidation (MnO_2; 95%) provided **9**. As required for isoiridomyrmecin, methylation of **9** under kinetic conditions (LDA, -78 °C; MeI) occurred with complete stereoselectivity to give the product of convex face attack (**8**) in 75% yield[8].

The reaction of **8** with $LiMe_2Cu$ at -78 °C and subsequent trapping of the enolate intermediate produced in quantitative yield a 4.5:1 mixture of the desired 1,5-β-addition product, **7**, and the 1,7-β-addition product, **11**, which were readily separated by chromatography (EtOAc-Et_2O 5:95) on silica-10% $AgNO_3$[8,9]. The ratio of **7** to **11** observed here suggests, in part, that the sterically unfavorable sp^3-sp^3 interaction (C6-C4) which develops in the 1,7-mode of addition, is more pronounced than the sp^3-sp^2 interaction (C8-C2) which arises in the 1,5-mode of addition[10]. In support of this point the corresponding conversion **3** → **2**, for which the analogous sp^3-sp^3 interaction (C6 hydrogen - C12 methyl) would be greater, occurred with complete regio- and stereospecificity, giving only the product of 1,5-addition[1d,6].



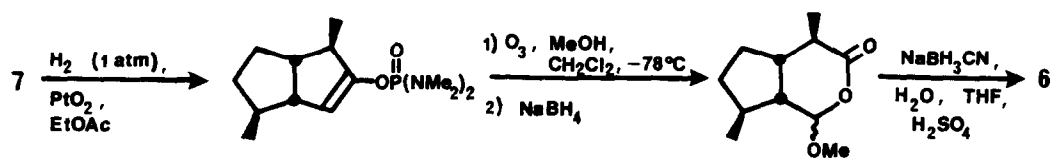
8 **7** **11**

It is of further importance to note that the stereochemical outcome of these reactions is most easily explained by approach of the cuprate reagent to the less hindered face of the tricyclo[3.3.0.0^{2,8}]octen-3-one system, presumably via a nucleophilic addition mechanism[11]. In further illustration of this point, ketone **4** upon reaction with $LiMe_2Cu$ gave exclusively the product (**12**) of convex face attack (as determined by difference NOE)[12] in good yield. An alternative mechanism involving initial single electron transfer[11], although perhaps unlikely because of the relatively large negative reduction potential expected for vinylcyclopropyl ketones[11], cannot be ruled out.



4 **12**

Final verification of the structure of **7** and completion of the synthesis of (±)-isoiridomyrmecin proceeded in a straightforward fashion. Thus, selective hydrogenation of **7** produced **13** (90% yield)[8], which upon ozonolysis in methanol with $NaBH_4$ workup gave a 1:1 mixture of anomeric pseudoesters **14** (92% yield)[8]. Reduction of **14** with $NaBH_3CN$ in acidified aqueous THF and flash chromatography provided analytically pure (±)-isoiridomyrmecin (68% yield), which was spectroscopically identical (IR, ^{1}HNMR, ^{13}CNMR) to an authentic sample of racemic isoiridomyrmecin kindly provided by Professor M. Vandewalle[4d,13].



13 **14**

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†Harvard University, Travelling Scholar 1981-83.

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7. Gilbert, A.; Samsudin, M.W. J. Chem. Soc., Perkin I, **1980**, 1118.

8. All new compounds gave satisfactory ^{1}HNMR, IR, and mass spectra and exact mass or combustion analyses.

9. For **11** (R=$PO(NMe_2)_2$): ^{1}HNMR (300 MHz), δ 5.60(1H, dt; J=5.6 Hz), 5.55(1H, dt; J=5.6 Hz), 5.16(1H, m), 3.70(1H, dm; J=7.7 Hz), 2.66(12H, q; J=4.9 Hz), 2.60-2.48(2H, bm), 1.94(1H, quintet; J_1=7.7 Hz, J_2=3.9 Hz, J_3=3.9 Hz), 1.16(3H, d; J=7.0 Hz), 1.06(3H, d; J=7.0 Hz). The C4 and C6 methyl stereochemical assignments were made on the basis of difference NOE experiments. Upon irradiation at 1.06 ppm and 1.16 ppm the 1.94 ppm methine exhibited 15.3% and 17.2% positive NOE, respectively. Upon irradiation at 1.94 ppm the following NOE's were observed: 3.70 ppm methine, 10.3%; 1.16 ppm methyl, 7.1%; 1.06 ppm methyl, 10.3%.

10. MM2 calculations indicate the following Van der Waals 1,5-interactions: **11** (R=H), C6 hydrogen - C4 hydrogen, 0.62 kcal; **7** (R=H), C8 hydrogen - C2 hydrogen, -0.05 kcal.

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12. For **12**: ^{1}HNMR (300 MHz) (partial), δ 5.59(1H, dd; J_1=5.6 Hz, J_2=2.7 Hz), 5.43(1H, dd; J_1=5.6 Hz, J_2=1.9 Hz), 2.63(1H, qt; J=7.4 Hz), 1.92(1H, m; CH_2), 1.42(1H, m; CH_2), 1.06(3H, d; J=7.4 Hz). Upon irradiation of the 1.06 ppm methyl the following NOE's were observed: 5.43 ppm vinyl, 5.0%; 2.63 ppm methine, 10.9%; 1.92 ppm methylene, 4.8%. Upon irradiation at 1.9 ppm the following NOE's were observed: 1.42 ppm methylene, 16.6%; 1.06 ppm methyl, 4.7%.

13. We thank Professor Vandewalle (State University of Ghent) for his generous gift of a comparison sample.

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