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A Formal Synthesis of (+)-Juvabione[1]

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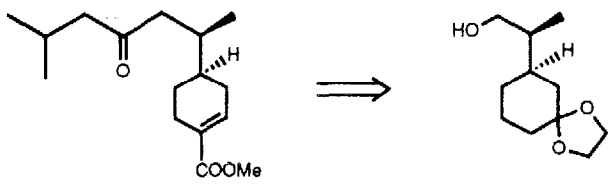
Key Words: Juvabione, asymmetric, diastereoselective, organomanganese arene complex, nucleophile

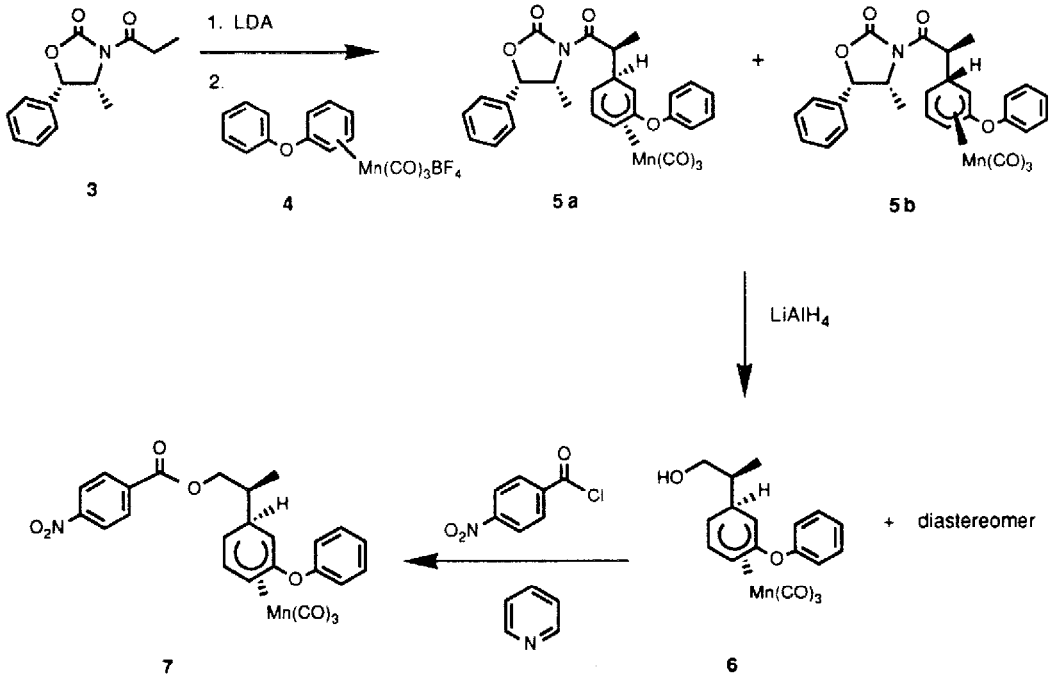
Abstract: *A formal synthesis of (+)-juvabione is presented based on the diastereoselective addition of the enolate of N-acyloxalidinone 3 with* η^6-$(C_6H_5OC_6H_5)Mn(CO)_3BF_4$.

The reaction of organotransition metal complexes with nucleophiles offers a powerful method in the formation of carbon-carbon bonds.[2] The addition of chiral nucleophiles to achiral transition metal electrophiles has received increasing attention as a method for the synthesis of asymmetric compounds.[3,4] For example, the addition of chiral nucleophiles to organomanganese arene complexes gives chiral η^5-dienyl complexes which have been converted into enantiomerically enriched α-arylglycine derivatives[4a] and 2-arylpropionic acids.[4b] Although the oxidative-demetallation of chiral η^5-dienyl manganese complexes allows facile access to chiral aromatic compounds, the further functionalization of these complexes into η^4-diene complexes[5-7] offers the exciting possibility for the synthesis of chiral cyclohexadiene derivatives. In our recent enantioselective synthesis of (S)-2-(3-phenoxyphenyl)propionic acid (Fenoprofen),[4b] we serendipitously discovered a small but appreciable stereoselectivity in the formation of the chiral center at the ring carbon. We reasoned that further functionalization of the η^5-dienyl manganese complex using Sweigert's procedure[5] would allow us to synthesize sesquiterpenes such as (+)-juvabione **1**,[8-11] a highly active juvenile hormone. Herein we describe the synthesis of **2** in enantiomerically pure form, establishing a formal synthesis of (+)-juvabione.

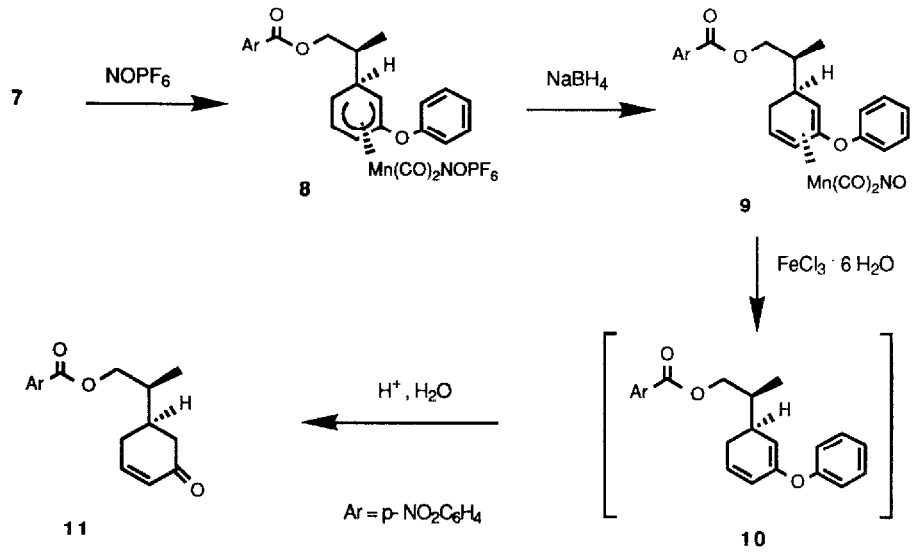


1 **2**

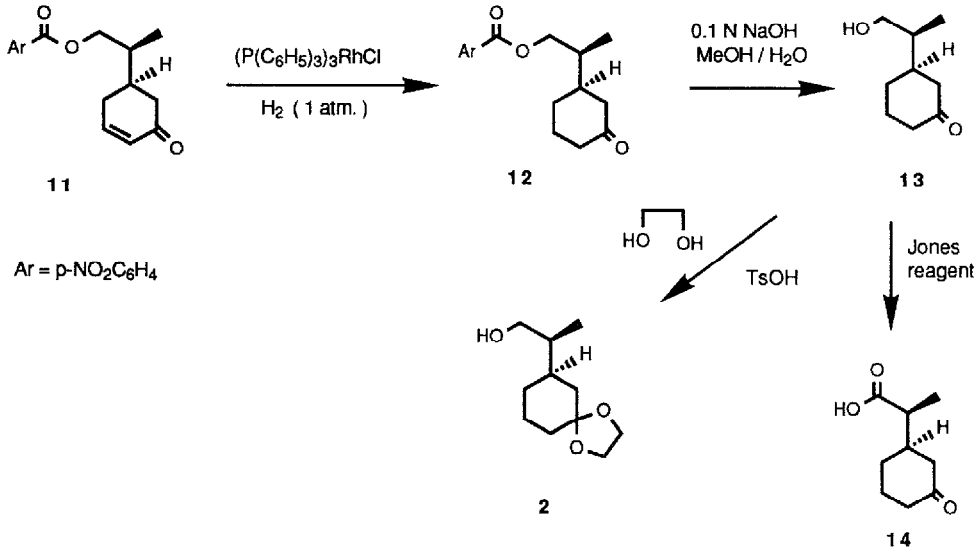
The reaction of the lithium enolate of **3** with η^6-$(C_6H_5OC_6H_5)Mn(CO)_3BF_4$ (rapid addition of **4** to the enolate of **3** in THF at -78°C, warmed to 0°C over 0.5 hr) gave η^5-dienyl complex **5** (76% yield; **5a**:**5b**, 3.5:1).[4b] The unexpected selectivity was diminished when **4** was added to the enolate of **3** more slowly. Our attempts to prepare the cationic η^5-dienyl complex from **5** ($NOBF_4$ or $NOPF_6$ in CH_2Cl_2)[5] regenerated the η^6-arene complex **4**. Therefore the inseparable η^5-dienyl complexes **5a** and **5b** were subjected to reductive removal of the chiral auxiliary (1.1 equiv $LiAlH_4$, Et_2O, 0°C, 1 hr; 65% yield) to give alcohol complex **6** and its diastereomer.[12] The alcohol complexes were immediately converted into the corresponding 4-nitrobenzoate esters (4-nitrobenzoyl chloride, pyridine, C_6H_6; greater than 90% yield). The diastereotopic esters were readily separated by recrystallization (CH_2Cl_2/hexane; 63% yield of **7** based on the alcohol complexes, greater than 95% d.e.).



The reactivation of the η^5-dienyl moiety, nucleophilic attack by hydride, and decomplexation were performed at this stage. Complex **7** gave nitrosyl complex **8** ($NOPF_6$, 1.1 equiv, CH_2Cl_2, 0°C, 1 hr: 74% yield) with no evidence of the removal of the exo-moiety. The regioselective addition of $NaBH_4$ (1.4 equiv, -5°C, 6 hrs) gave η^4-diene complex **9** (65% yield). Following procedures for the demetallation of related η^4-diene metal complexes,[5d] $FeCl_3 \cdot 6H_2O$ (6 equiv) in THF gave clean removal of the diene moiety. The readily hydrolyzed 2-phenoxydiene **10** was directly converted (H_2O, H^+) into cyclohexenone **11** (84% yield for the two steps). We did not observe epimerization during this reaction sequence.



Cyclohexenone **11** was hydrogenated (1 atm of H_2, 0.1 equiv of $(P(C_6H_5)_3)_3RhCl$, 25°C, 12 hrs) to give cyclohexanone **12** (95% yield). Saponification (0.1 M NaOH; CH_3OH:H_2O, 1:1) of the 4-nitrobenzoate moiety of **12** gave keto-alcohol **13** (98% yield).[13] Conversion of the ketone into its ethylene glycol ketal ($HOCH_2CH_2OH$, TsOH) gave **2** (90% yield), establishing a formal synthesis of (+)-juvabione. Oxidation (Jones reagent, acetone) of keto-alcohol **13** gave keto-acid **14** (60% yield) which allowed the unequivocal assignment of the relative stereochemistry by ^{13}C NMR.[11f] The stereochemical assignment of **14** allowed the definitive stereochemical assignment of the intermediates in this synthesis.



Further applications for the enantiospecific synthesis of natural products as well as investigations into the origin of the diastereoselectivity for the reaction of chiral enolates with organomanganese arene complexes is continuing and will be reported in due course.

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12. All new stable compounds were characterized by IR, ^{1}H and ^{13}C, and C/H analysis. Representative spectral data: For **7a**: ^{1}H NMR (C_6D_6) 7.67 (2H, d, J=9.1 Hz), 7.65 (2H, d, J=9.1 Hz), 6.8-7.2 (5H, m), 5.31 (1H, dd, J=1.5, 5.6 Hz), 4.11 (1H, t, J=6.4 Hz), 3.90 (1H, dd, J=4.7, 11.1 Hz). 3.77 (1H, dd, J=4.7, 6.0 Hz), 2.88 (1H, m), 2.37 (1H, m), 2.12 (1H, m), 0.82 (1H, m); IR (CH_2Cl_2) 2022, 1942, 1802, 1724 cm^{-1}. For **9**: ^{1}H NMR (C_6D_6) 7.79 (2H, d, J=9.0 Hz), 7.68 (2H, d, J=9.0 Hz), 6.87-7.23 (5H, m), 4.84 (1H, dd, J=1.8, 8.1 Hz), 4.01 (2H, m), 3.45 (1H, t, J=2.8 Hz), 2.29 (1H, m), 1.94 (1H, m), 1.65 (1H, m), 1.35 (1H, m), 0.91 (1H, m), 0.75 (3H, d, J=6.9 Hz); IR (CH_2Cl_2) 2037, 1983, 1736 cm^{-1}. For **11**: ^{1}H NMR ($CDCL_3$) 8.30 (2H, d, J=9.0 Hz), 8.19 (2H, d, J=9.0 Hz), 7.01 (1H, m), 6.07 (1H, d, J=10.5 Hz), 4.39 (1H, dd, J=6.0, 11.2 Hz), 4.28 (1H, dd, J=6.1, 11.2 Hz), 2.0-2.6 (6 H, m), 1.10 (3H, d, J=6.9 Hz); IR (CH_2Cl_2) 1724, 1678, 1604 cm^{-1}.
13. Conversion of **13** into the corresponding Mosher's ester gave a single diastereomer as determined by ^{1}H NMR and GC.

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