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A Stereoselective Total Synthesis of (±)-Erythrodiene

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Abstract: Erythrodiene, a unique spirobicyclic sesquiterpene hydrocarbon from the Caribbean gorgonian coral *Erythropodium caribaeorum*, has been synthesized from 4-isopropylcyclohexanol in 8-steps and approximately 16% overall yield. The synthesis features a stereoselective intramolecular carbomercuration reaction as the key step.

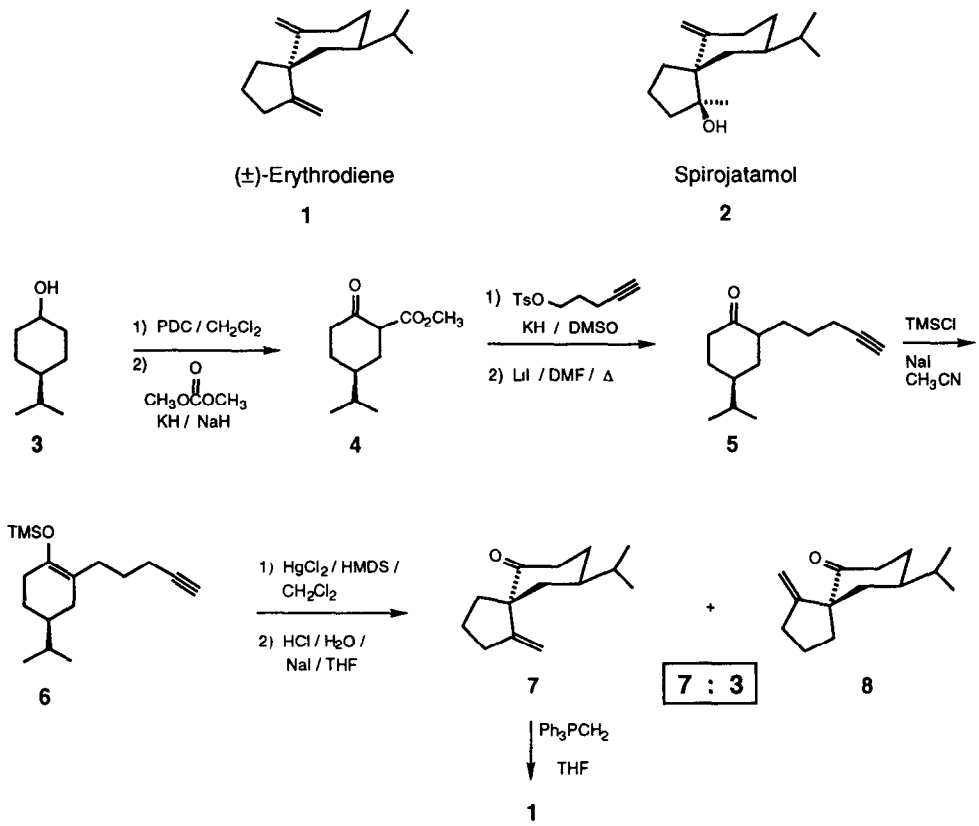
Erythrodiene (**1**) is a unique spirobicyclic sesquiterpene hydrocarbon that has been isolated recently from the Caribbean gorgonian coral *Erythropodium caribaeorum*.[1] The terrestrial natural product spirojatamol[2] (**2**) is one of the few compounds known to share the spirobicyclo[5.4]decane skeleton of erythrodiene. We have developed an efficient and stereoselective synthesis of this novel spirobicyclic sesquiterpene skeleton and report here its application to the total synthesis of (±)-erythrodiene.

Our approach to assemble the isopropyl substituted spirobicyclo[5 4]decane system of erythrodiene was to stereoselectively form the spiro ring fusion using an intramolecular carbomercuration reaction. This modification of the Conia reaction has been shown previously to be useful for the efficient formation of simple monocyclic and fused ring systems under mild conditions.[3-5] In continuing to examine the scope and synthetic utility of these types of reactions, we have found that more highly functionalized spirocyclic systems may be constructed with a useful degree of stereoselectivity.

The synthesis of erythrodiene began with 4-isopropylcyclohexanol (**3**) This was converted into the corresponding β-keto ester (**4**) by PDC oxidation followed by treatment with dimethylcarbonate and NaH / KH,[6] as illustrated in the scheme. Alkylation and decarboxylation gave ε-alkynyl ketone **5** as a mixture of α-keto epimers Regioselective enol ether formation[7] followed by silica gel chromatography provided cyclization precursor **6**, which was shown to be free of the regioisomeric enol ether by ^{1}H NMR spectroscopy. Alkynyl enol ether **6** was cyclized efficiently by treatment with $HgCl_2$ (1.1 equiv) and hexamethyldisilazane (0.2 equiv) in CH_2Cl_2 (40 min, 25 °C)[3] The resultant vinyl mercurial cyclization products could be isolated and chromatographically separated, or proto-demercuration could be effected *in situ* by the addition of 5M aqueous HCl (2 equiv), NaI (3 equiv), and THF to the reaction mixture (0 to 25 °C, 1 h). *In situ* protonolysis followed by work-up and chromatography gave the two isomeric β-vinyl ketones **7** and **8** respectively in 69% and 27% yield based on **6**.[8]

The major product of carbomercuration / proto-demercuration (**7**) was converted into (±)-erythrodiene (**1**)[9] in 74% yield using $(Ph)_3PCH_2$ in THF. Similar treatment of the minor product (**8**) led to the distereomeric diene Interestingly, the intramolecular carbomercuration reaction preferentially leads to the axial β-keto vinyl mercurial cyclization product and provides the spirobicyclic sesquiterpene system of erythrodiene and spirojatamol. We are continuing to study the basis of the observed stereoselectivity, as well as methods to enhance the synthetic utility of these exceptionally mild and efficient carbon-carbon bond forming processes.

Scheme



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References and Notes

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8. The structures of **7** and **8** were tentatively assigned on the basis of the relative chemical shift differences of the vinyl proton resonances in the ^{1}H NMR spectra (300 MHz, $CDCl_3$); **7**: δ 5.11 and 5.03; **8**: δ 5.12 and 4.78. The assignment for **7** was confirmed by the conversion of **7** into **1**.
9. The spectral data (^{1}H and ^{13}C NMR, LREIMS, and HREIMS) of the synthetic product matched those of the natural product. [Note: The ^{13}C NMR resonance reported at δ109.9 in reference 1 is a typographical error (Prof. Fenical, personal communication) and actually occurs at δ105.9.]

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