A Simple Total Synthesis of (±)-Spirojatamol and (±)-Erythrodiene *via* Intramolecular 1,3-Dipolar Cycloaddition

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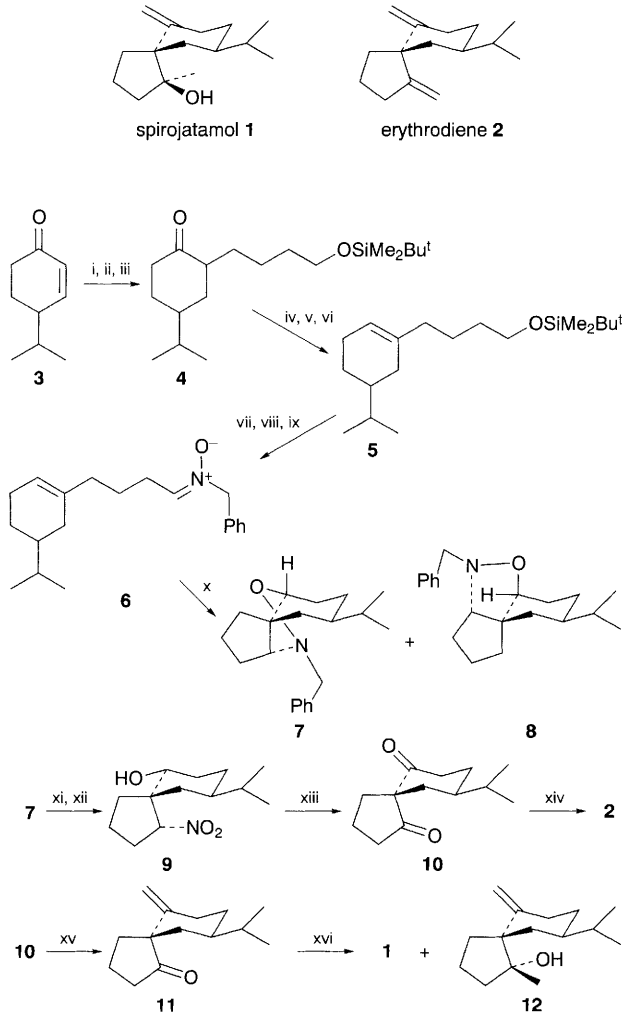
An efficient synthesis of spirobicyclic sesquiterpenes, (±)-spirojatamol **1** and (±)-erythrodiene **2**, using an intramolecular 1,3-dipolar cycloaddition as the pivotal step is described.

Spirobicyclic sesquiterpenes have received growing interest because of their unique carbon skeleton. Spirojatamol **1**,[1] isolated from the roots of *Nardostachys jatamansi*, and erythrodiene **2**,[2] found in the encrusting Caribbean gorgonian coral *Erythropodium caribaeorum*, have a spirobicyclo-[5.4]decane framework. It is considered that the biosynthesis of these natural products is different from that of other spirobicyclic sesquiterpenes. Huang and Forsyth reported a total synthesis of (±)-**2** by way of an intramolecular carbomercuration reaction as the key step.[3] We planned a new approach to these natural products *via* the isoxazolidine **7** which could be constructed by an intramolecular 1,3-dipolar cycloaddition[4] of the nitrone **6**. Here, we describe a facile total synthesis of the racemates of spirojatamol **1** and erythrodiene **2**.



Scheme 1 *Reagents and conditions*: i, 10% Pd–C, H_2 (1 atm); ii, cyclohexylamine; iii, LDA, HMPA, 4-*tert*-butyldimethylsiloxybutyl bromide; iv, Me_3SiI, $(Me_3Si)_2NH$; v, MeLi, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]pyridine; vi, $Pd(PPh_3)_2(OAc)_2$, HCO_2H, NBu^n_3; vii, H_3O^+; viii, Me_2SO, SO_3·py, NEt_3; ix, $PhCH_2NHOH$, $MgSO_4$; x, heat; xi, 10% Pd–C, H_2 (6 atm); xii, MPBA, Na_2CO_3; xiii, TPAP, NMO; xiv, Zn–CH_2Br_2–$TiCl_4$; xv, $Ph_3P{=}CH_2$; xvi, MeMgBr

The readily available 4-isopropylcyclohexenone **3**[5] was converted, by catalytic hydrogenation and cyclohexylamine treatment, into the corresponding enamine, which was treated with LDA in the presence of hexamethylphosphoric triamide (HMPA) and then a 4-siloxybutyl bromide to give **4** as two diastereoisomers in 88% overall yield from **3**. High regioselectivity (97 : 3) was obtained in the formation of the enol silyl ethers from **4** using trimethylsilyl iodide in the presence of hexamethyldisilazane at 0 °C.[6] Treatment of the resulting enol silyl ethers with MeLi in DME at 0 °C, followed by reaction with *N*-(2-pyridyl)triflimide,[7] provided the corresponding enol triflate in 88% yield. Reduction of the enol triflate with $Pd(PPh_3)_2(OAc)_2$ in the presence of NBu^n_3 and HCO_2H[8] furnished **5**, ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 5.37 (br s), in 94% yield. The olefin **5** was transformed into the nitrone **6**, mp 72–73 °C, in 66% overall yield through a three-step sequence consisting the deprotection of the $SiMe_2Bu^t$ group, oxidation by Parikh's procedure,[9] and reaction with *N*-benzylhydroxylamine.[10] The intramolecular [3 + 2] nitrone–olefin cycloaddition reaction was carried out by heating **6** in toluene at 180 °C in a sealed tube for 22 h to produce two stereoisomers **7** (33%) and **8** (22% yield).†

The major diastereoisomer was assigned to the desired structure **7** based on the energy difference of 0.38 kcal mol^{-1} (1 cal = 4.184 J) between **7** and **8** using molecular mechanics (MMX) calculations.[11] Reduction of **7** with 10% Pd–C under H_2 (6 atm) produced the amino alcohol. Since direct oxidation of the amino group to the carbonyl group gave poor results, the amine was first oxidized with MCPBA[12] to the nitro alcohol **9**, mp 147–149 °C, in 47% overall yield from **7**. Oxidation of **9** with tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) afforded the diketone **10** in 81% yield.[13] (±)-Erythrodiene **2** was prepared from **10** in 34% yield using the method of Nozaki and Lombardo.[14] On the other hand, a high regioselective olefination of **10** (55% yield, 77% yield based on recovered starting material) forming **11** was achieved by the usual Wittig reaction. The Grignard reaction of the resulting olefinic ketone **11** gave a separable 1.1 : 1 mixture of **1** and the stereoisomer **12** (62% yield, 81% yield based on recovered starting material). The IR, ^{1}H NMR, ^{13}C NMR and MS spectral data of (±)-**1** and (±)-**2** were identical with those of the authentic compounds.[1,3]

Thus, total syntheses of (±)-spirojatamol **1** and (±)-erythrodiene **2** have been accomplished through construction of the spirobicyclo[5.4]decane system by intramolecular 1,3-dipolar cycloaddition.

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Footnote

† All new compounds gave satisfactory spectral data (IR, NMR and MS) and microanalytical or high-resolution MS data. *Selected data* for **7**: NMR; δ_H (500 MHz, $CDCl_3$) 0.807 (3 H, d, *J* 6.7 Hz, CH*Me*), 0.811 (3 H, d, *J* 6.7 Hz, CH*Me*), 2.94 (1 H, br d, *J* 4.9 Hz, CHNO), 3.66 (1 H, dd, *J* 3.1 and 3.1 Hz, CHO), 3.97 (1 H, d, *J* 13.4 Hz, C*H*HPh), 4.06 (1 H, d, *J* 13.4 Hz,

CH*H*Ph), 7.23–7.40 (5H, m, Ph). For **8**: NMR; δ_H (500 MHz, $CDCl_3$) 0.85 (6 H, d, *J* 6.7 Hz, CH*Me*$_2$), 2.90 (1 H, br d, *J* 6.1 Hz, CHNO), 3.66 (1 H, br d, *J* 1.8 Hz, CHO), 3.98 (1 H, d, *J* 12.8 Hz, C*H*HPh), 4.23 (1 H, d, *J* 12.8 Hz, CH*H*Ph), 7.23–7.43 (5 H, m, Ph). For **9**: IR ν_{max}/cm^{-1} (neat) 3320, 1550 and 1370; NMR, δ_H (300 MHz, $CDCl_3$) 0.87 (6 H, d, *J* 6.6 Hz, CH*Me*$_2$), 3.60 (1 H, br dd, *J* 4.6 and 11.2 Hz, CHO), 4.94 (1 H, br d, *J* 5.9 Hz, $CHNO_2$). For **10**: IR ν_{max}/cm^{-1} (neat) 1725 and 1688; NMR, δ_H (500 MHz, $CDCl_3$) 0.88 (3 H, d, *J* 7.1 Hz, CH*Me*), 0.90 (3 H, d, *J* 6.4, CH*Me*). For **11**: IR: ν_{max}/cm^{-1} (neat) 1730 and 1635; NMR, δ_H (300 MHz, $CDCl_3$) 0.83 (3 H, d, *J* 6.6 Hz, CH*Me*), 0.85 (3 H, d, *J* 6.6 Hz, CH*Me*), 4.78 (1 H, br s, =CH*H*), 4.85 (1 H, br s, =C*H*H).

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