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A Total Synthesis of (±)-Hispanolone†

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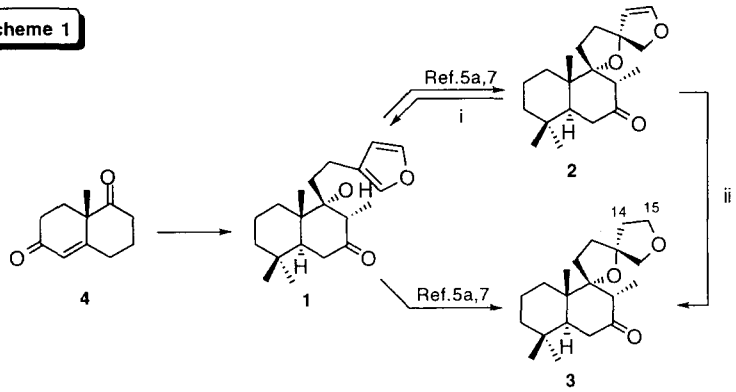
Abstract: Hispanolone (**1**), employed recently in our partial synthesis of the specific platelet activating factor antagonist prehispanolone (**2**), was prepared from (±)-Wieland-Miescher ketone (**4**).

Hispanolone (**1**) was obtained from *Ballota hispanica* for the first time in 1978,[1] and was subsequently employed as a precursor in the preparation of drimane derivatives.[2] The conversions of **1** to a perfumery substance, namely ambreinolide and to other drimane sesquiterpenoids have also been described recently.[3]

Scheme 1



i, 0.5% HCl, EtOAc, (100%); ii, H_2, 5% Pd-C, EtOAc, (91%)

In 1994, our laboratory disclosed the isolation and identification of hispanolone (**1**) and prehispanolone (**2**) from the aerial parts of *Leonurus heterophyllus* (Yi Mu Cao),[4,5d] It is essential to note that **1** was also obtained efficiently through a mild acid hydrolysis of prehispanolone (**2**).[4,5d] Using an *in vitro* radioligand binding assay for the platelet activating factor (PAF) receptor,[6] compound **2** was identified as a specific PAF

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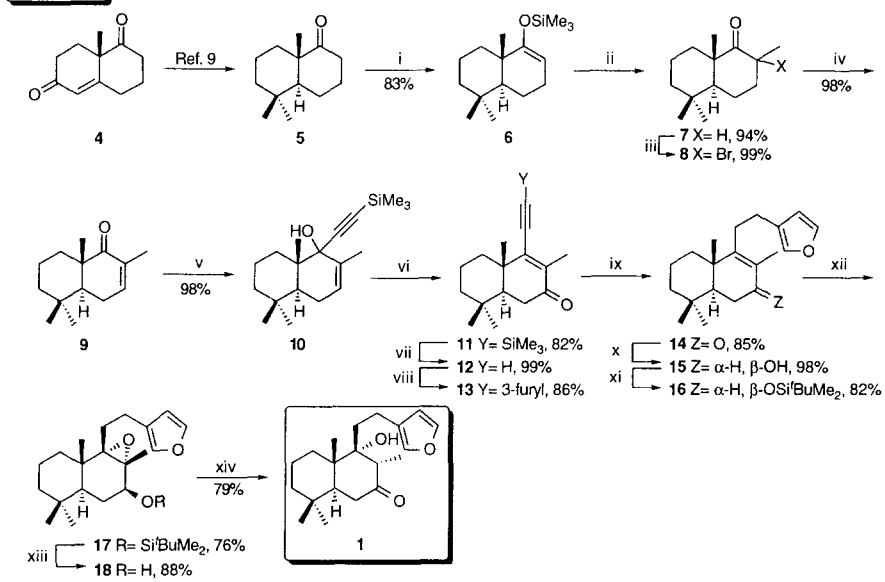
receptor antagonist.[5c] Furan **1**, on the other hand, did not exhibit any observable activity in the same bioassay. Moreover, catalytic hydrogenation of **2** converted it to the acid-insensitive and bioactive 14,15-dihydroprehispanolone (**3**).[5c,5d] It appears now that both **2** and **3** are good leads for a structure-activity relationship study and further pharmacological evaluation.

Because of its relative structural simplicity as well as its ready availability, hispanolone (**1**) served as a pivotal intermediate *en route* to our partial synthesis of **2** and **3**.[5a,7] In order to complete the total synthesis of compound **2** and **3**, herein we report a synthetic route to construct the precursor, hispanolone (**1**), from (±)-Wieland-Miescher ketone.

Scheme 2



i, LDA, Me_3SiCl, THF, 0°C to r.t.; ii, MeI, TBAF, 4Å molecular sieves, THF, r.t.; iii, $C_5H_6Br_3N$, HOAc, r.t.; iv, DBU, PhMe, reflux; v, lithium trimethylsilylacetylide, Et_2O, -78°C to r.t.; vi, PCC, florisil, CH_2Cl_2, r.t.; vii, K_2CO_3, MeOH, r.t.; viii, 3-bromofuran, $Pd(PPh_3)_4$, CuI, Et_2NH, reflux; ix, H_2, 10% Pd-C, 0.2N KOH in MeOH; x, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C; xi, imidazole, $^tBuMe_2SiCl$, MeCN, 0°C to r.t.; xii, MCPBA, $NaHCO_3$, CH_2Cl_2, 0°C; xiii, TBAF, THF, 0°C to r.t.; xvii, (a) LAH, Et_2O, r.t. (b) PDC, 4Å molecular sieves, CH_2Cl_2, r.t.

As shown in Scheme 2, the commercially available (±)-Wieland-Miescher ketone (**4**)[8] was converted to ketone **5** by modifying the method reported by Sondheimer and Elad.[9] A seemingly straightforward mono-methylation of compound **5** with lithium diisopropylamide and iodomethane in tetrahydrofuran at between -78°C and room temperature was however unsuccessful, providing a chromatographically inseparable mixture of mono- and di-methylated compounds. In order to alleviate the need for tedious chromatography, a two-step procedure,[10] i.e., silyl enol ether formation and desilylation-methylation, was engaged for the introduction of a methyl group at the α-position of compound **5**, leading to **7** in an acceptable overall yield. Bromination of the α-methyl ketone **7** with pyridinium bromide perbromide (PBB) in acetic acid[11] afforded the α-bromo-α-methyl ketone **8**. Dehydrobromination of compound **8** with DBU in dry toluene at refluxing temperature[12] converted **8** to enone **9**. After an 1,2-addition of lithium trimethylsilylacetylide to **9**, the resulting tertiary alcohol **10** was

allowed to undergo 1,3-alcohol transposition and subsequent oxidation, utilizing PCC[13] to provide the α,β-unsaturated ketone **11**.[14] Desilylation of **11** gave the unstable compound **12**, which was found to decompose gradually within 48 hr at room temperature. For this reason, coupling between compound **12** and 3-bromofuran by employing the Sonogashira coupling reaction condition[15] was carried out immediately after **12** was purified by column chromatography on silica gel.

Catalytic hydrogenation[16] of furan **13** in the presence of 10% palladium-charcoal led quantitatively to enone **14**.[14] Noteworthy is the fact that over-hydrogenation of enone **14** is possible if the reaction condition was not carefully controlled. Enone **14** is a known molecule obtained previously through dehydration of **1**.[17] Thus, the structure of **14** was substantiated by comparison of its ^{1}H NMR, ^{13}C NMR and mass spectra with those of the known compound.[17]

Encouraged by the aforementioned results, we therefore set forth to complete our synthesis of **1**. Despite much experimentation, we were unable to epoxidize the enone **14** in a simple manner, presumably due to the steric hindrance of the tetrasubstituted alkene. Another avenue in which **14** could be converted to **1** would be the use of a multi-step pathway. Thus the carbonyl group of compound **14** was selectively reduced with sodium borohydride in the presence of cerium(III) chloride heptahydrate[18] to furnish **15**, whose hydroxyl group should be β due to the appearance of a triplet for H-7 at δ 3.90 (J = 7.5 Hz) in its ^{1}H NMR spectrum.[17a] The C-7 hydroxyl group was then protected as *t*-butyldimethylsilyl ether, providing **16**. The carbon-carbon double bond of **16** was successfully epoxidized using *m*-chloroperbenzoic acid under buffered conditions,[19] leading to epoxide **17**. After desilylation, the resulting alcohol **18**[14] was reduced with lithium aluminum hydride in diethyl ether at room temperature[20] to afford a diol, which was not purified further because of its instability to column chromatography, but was oxidized to give the desired target molecule, namely hispanolone (**1**).[14] The spectroscopic data of the synthetic **1** are in full agreement with those of the naturally occurring hispanolone (**1**).[14] The total synthesis of the enantiomerically pure form of hispanolone (**1**) from commercially available (*S*)-(+)-Wieland-Miescher ketone is now in progress in our laboratory.

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† Dedicated to Professor Emanuel Vogel on the occasion of his 70th birthday.

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14. Compound **11**: white needle-shaped crystals; m.p. 56-58°C; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H, Me-17), 1.16 (s, 3H, Me-18 or Me-19 or Me-20), 0.90 (s, 3H, Me-18 or Me-19 or Me-20), 0.87 (s, 3H, Me-18 or Me-19 or Me-20), 0.21 (s, 9H, Si-Me_3); ^{13}C NMR ($CDCl_3$) δ –0.39, 13.97, 18.51, 18.66, 20.88, 32.10, 32.85, 35.05, 37.31, 38.92, 40.97, 49.84, 100.73, 111.62, 137.15, 149.25, 199.05. Compound **14**: white needle-shaped crystals; m.p. 54-55°C; ^{1}H NMR ($CDCl_3$) δ 7.67 (d, *J* 0.6Hz, 1H, H-16), 7.40 (t, *J* 1.5Hz, 1H, H-15), 6.46 (d, *J* 1.2, 1H, H-14), 1.95 (s, 3H, Me-17), 1.19 (s, 3H, Me-18 or Me-19 or Me-20), 0.90 (s, 3H, Me-18 or Me-19 or Me-20), 0.87 (s, 3H, Me-18 or Me-19 or Me-20). ^{13}C NMR ($CDCl_3$) δ 11.47, 18.11, 18.60, 21.31, 24.21, 30.19, 32.52, 33.14, 35.24, 35.88, 40.90, 41.29, 50.27, 110.58, 124.51, 130.34, 138.64, 143.04, 167.10, 200.37. Compound **18**: oil; ^{1}H NMR ($CDCl_3$) δ 7.34 (t, 1H, *J* 1.5 Hz, H-15), 7.21 (s,1H, H-16), 6.26 (d, *J* 0.9 Hz, 1H, H-14), 3.90 (t, *J* 8.7Hz, 1H, H-7), 1.34 (s, 3H, Me-17), 1.07 (s, 3H, Me-18 or Me-19 or Me-20), 0.83 (s, 3H, Me-18 or Me-19 or Me-20), 0.85 (s, 3H, Me-18 or Me-19 or Me-20); ^{13}C NMR ($CDCl_3$) δ 16.95, 17.40, 18.33, 21.49, 21.61, 27.19, 28.68, 32.67, 33.45, 34.45, 38.79, 40.21, 41.27, 64.59, 70.00, 72.13, 110.87, 125.00, 138.54, 142.76. These data are identical to those of the known compound reported in ref. 17(a). Compound **1**: white needle-shaped crystals; m.p. 140-142°C; ^{1}H NMR ($CDCl_3$) δ 7.36 (t, *J* 1.5Hz, 1H, H-15), 7.23 (s, 1H, H-16), 6.27 (d, *J* 0.9, 1H, H-14), 2.74 (q, *J* 6.6Hz, 1H, H-8), 1.18 (s, 3H, Me-18 or Me-19 or Me-20), 1.19 (d, *J* 6.6Hz, 3H, Me-17), 0.90 (s, 3H, Me-18 or Me-19 or Me-20), 0.88 (s, 3H, Me-18 or Me-19 or Me-20). ^{13}C NMR ($CDCl_3$) δ 8.25, 16.24, 18.51, 21.40, 21.56, 31.91, 33.08, 33.60, 34.74, 39.26, 41.31, 43.28, 46.47, 50.92, 81.78, 110.68, 124.83, 138.58, 143.07, 211.94.
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