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Total Synthesis of (-)-Hispanolone and An Improved Approach Towards Prehispanolone

Wing Shun Cheung and Henry N. C. Wong*

Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China.

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Abstract: On the basis of the recently reported construction of (±)-hispanolone (**2**), the enantiomerically pure form of (-)-**2**, employed in our partial synthesis of the specific platelet activating factor receptor antagonist prehispanolone (**3**), was prepared from (*S*)-(+)-Wieland-Miescher ketone (**1**). Moreover, an improvement of the literature synthesis *en route* to prehispanolone (**3**) starting from synthetic (-)-hispanolone (**2**) was also carried out.

Keywords: Cyclic Ketones; Furans; Lithiation; Terpenes.

Introduction

Hispanolone (**2**) was first isolated in 1978 from *Ballota hispanica*.[1] Since then, transformation of **2** into galeopsin was reported, together with some of its retro-aldol reaction and other ring B conversions.[2] Two years later, other transformations of **2** were also recorded.[3] In addition, the conversions of the readily available **2** to the perfumery substance ambreinolide and to drimane sesquiterpenoids were also outlined in the literature.[4]

The isolation and identification of hispanolone (**2**) and prehispanolone (**3**) from the acetone extract of aerial parts of *Leonurus heterophyllus* Sweet (Yi Mu Cao) was recently achieved in our laboratory.[5] The latter was characterized as a specific PAF receptor antagonist[6] through the examination of an *in vitro* radioligand binding assay for the platelet activating factor (PAF) receptor.[7] Compound **3** is able to inhibit ^{3}H-platelet activating factor binding to rabbit platelet membranes with an IC_{50} of 4 X 10^{-6} M,[5a] the concentration of drug being required to give a 50% inhibition of specific ^{3}H-PAF binding.[8] In contrast, hispanolone (**2**), obtained alternatively through the acid treatment of **3**,[5,9] was inactive in the same bioassay. As such, the existence of the tetrahydrofuran ring might seemingly be a crucial factor for a potential PAF receptor antagonist.[7] Moreover, as shown in Scheme 1, the catalytic hydrogenation product of **3**, namely 14,15-dihydroprehispanolone (**4**), was identified as a much better ligand for the PAF receptor.[5] For this reason, it is essential to note that both **3** and **4** are good leads for a structure-activity relationship study and further pharmacological evaluation.

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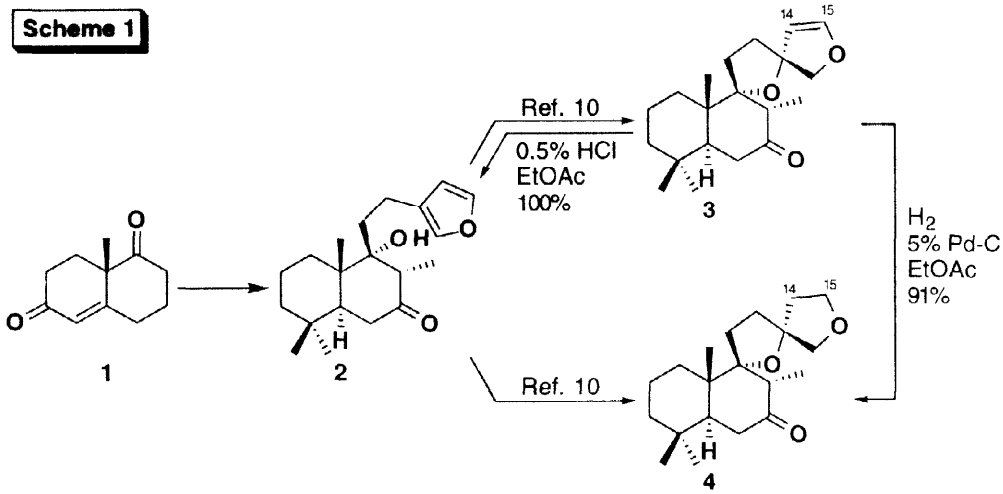
Scheme 1



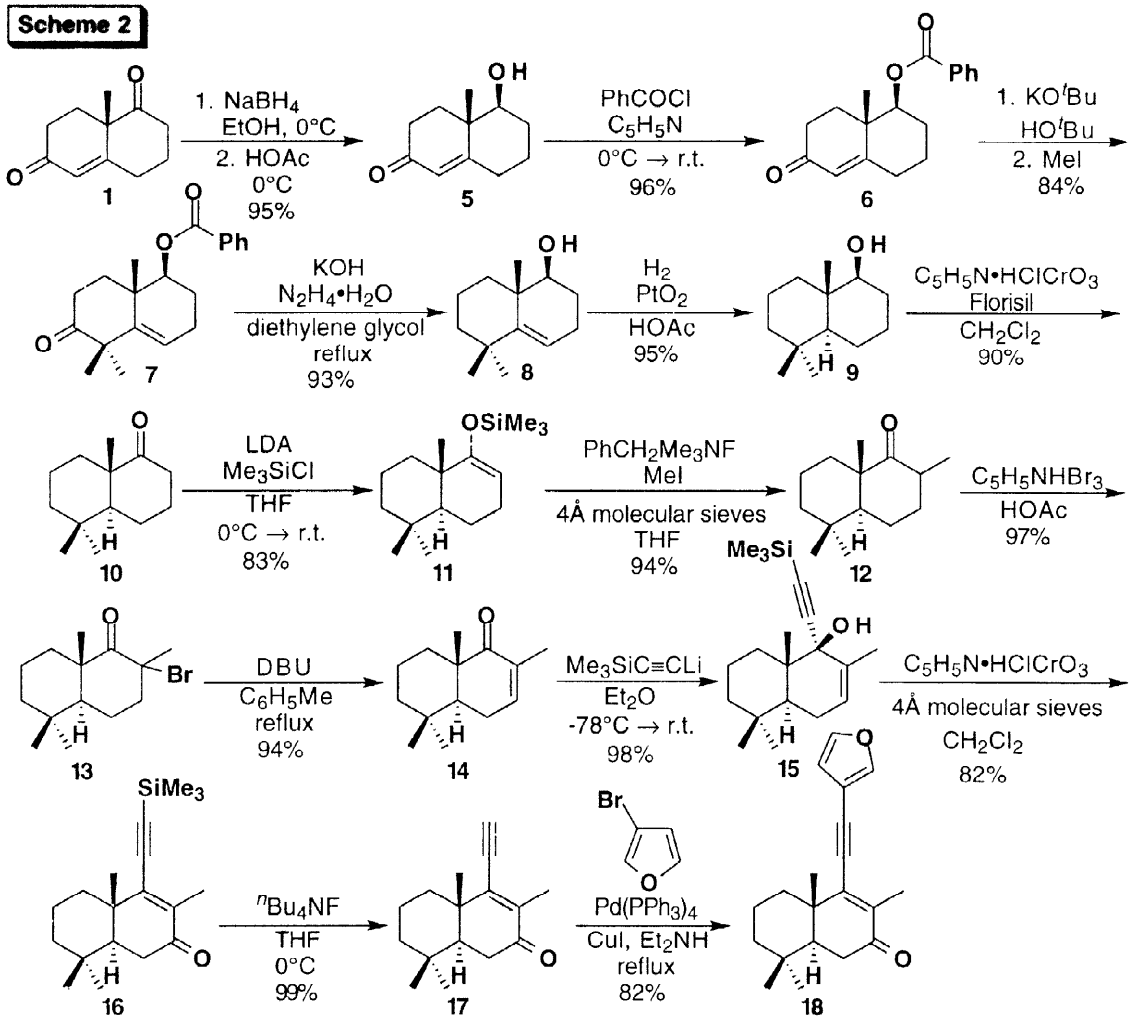
Because of its relative structural simplicity as well as its ready availability, hispanolone (**2**) served as a pivotal intermediate *en route* to our partial synthesis of **3** and **4**.[10] To establish a synthesis of hispanolone (**2**) and to complete the total synthesis of **3** and **4**, herein we report a synthetic route to assemble hispanolone (**2**) from the commercially available starting material, (*S*)-(+)-Wieland-Miescher ketone (**1**) (Scheme 1).

Results and Discussion

As reported previously, a more inexpensive racemic form of the Wieland-Miescher ketone (**1**) was used as the starting material for the synthesis of the optically inactive form of hispanolone (**2**).[11] In this report, a similar synthetic strategy for the realization of hispanolone (**2**) in an enantiomerically pure form is described (Scheme 2). Thus, a selective reduction of the keto group of (*S*)-(+)-Wieland-Miescher ketone (**1**) by sodium borohydride in EtOH provided the hydroxyl enone **5**, which was then protected with benzoyl chloride in pyridine to furnish the ester **6**. Dimethylation was then employed to convert **6** into α,α-dimethyl ketone **7** by treatment of **6** with potassium *tert*-butoxide and subsequently with methyl iodide in *tert*-butanol. The keto group of compound **7** was reduced and the benzoyl protection removed to give the unsaturated alcohol **8** on treatment with potassium hydroxide, hydrazine hydrate and diethylene glycol at reflux. Catalytic hydrogenation of compound **8** in the presence of the Adams' catalyst, palladium(IV) oxide, converted it to the saturated alcohol **9**. Oxidation of **9** with pyridinium chlorochromate (PCC) on Florisil afforded ketone **10**. The aforementioned six-step sequential transformations of (*S*)-(+)-Wieland-Miescher ketone (**1**) to the intermediate **10** was first reported by Sondheimer and Elad in 1957.[12b] The ^{1}H NMR and ^{13}C NMR spectra of ketone **10** as well as its mass spectrum are in full agreement with those reported in the literature.[12]

It is noteworthy that mono-methylation of the ketone **10** with lithium diisopropylamide and iodomethane was not trivial, providing instead a chromatographically inseparable mixture of mono- and di-methylated products. In order to alleviate the need for tedious column chromatography, a two-step procedure,[13] *i.e.*, silyl enol ether formation and desilylation-methylation, were engaged for the introduction of one methyl group to the α-position of ketone **10**. In practice, ketone **10** was first deprotonated with lithium diisopropylamide in tetrahydrofuran at 0°C and then the resulting enolate was silylated to furnish the silyl enol ether **11** with trimethylsilyl chloride at between 0°C and room temperature. The α-methyl ketone **12** was then conveniently obtained by dropping an anhydrous tetrahydrofuran solution of the resulting ether **11** into a stirred suspension of

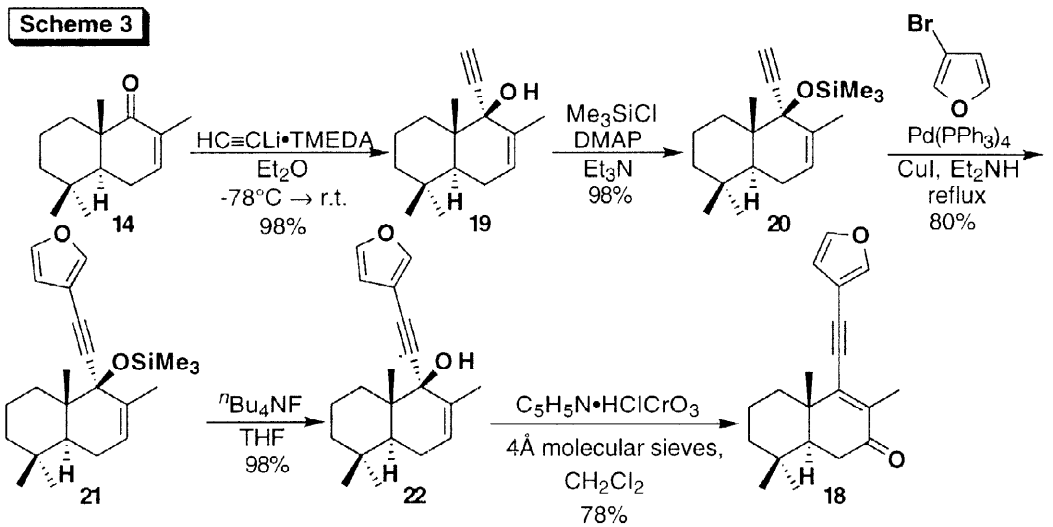
methyl iodide, benzyltrimethylammonium fluoride, and 4Å molecular sieves in anhydrous tetrahydrofuran. This two-step procedure proved to be satisfactory and provided an indirect avenue for the preparation of the mono-methylated product **12** in an acceptable 78% overall yield without any contamination of the α,α-dimethylketone.



Bromination of the α-methyl ketone **12** with pyridinium bromide perbromide in acetic acid[12a] expectedly afforded the α-bromo-α-methyl ketone **13**. Enone **14** was obtained through dehydrobromination of bromide **13** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry toluene at refluxing temperature.[14] An 1,2-nucleophilic addition of lithium trimethylsilylacetylide to enone **14** in diethyl ether at between -78°C and room temperature afforded the tertiary alcohol **15**. As indicated in the ^{1}H NMR spectrum of **15**, the regioselective 1,2-addition of lithium trimethylsilylacetylide to enone **14** was substantiated by the vinyl proton NMR signal that was shifted from δ 6.66 in enone **14** to the upfield region δ 5.42 in alcohol **15**. In addition, the structure of **15** was further verified by the disappearance of the carbonyl signal (δ 202.23 in enone **14**) and the existence of two sp^2 hybridized carbon signals (δ 123.51 and δ 135.18) in its ^{13}C NMR spectrum. A choice in favor of the C_1 stereochemistry of **15** as shown in Scheme 2 can be made on basis of the predominant α-nucleophilic attack because of the steric hindrance of the angular methyl group. However, it is clear that the α-alkynyl pattern was not crucial in the overall synthetic route because C_1 will become an alkenyl carbon in the ensuing steps. The

resulting tertiary alcohol **15** was allowed to undergo a 1,3-hydroxyl transposition and subsequent oxidation by utilizing pyridinium chlorochromate (PCC) and 4Å molecular sieves in dichloromethane, providing the α,β-unsaturated ketone **16**.[15] Enone **16** was then desilylated by employing tetrabutylammonium fluoride in tetrahydrofuran at 0°C to lead to the terminal alkyne **17**. In the absence of the trimethylsilyl moiety in **15**, the transposition product **17** was also obtained, albeit in a lower 58% yield, presumably due to the terminal alkyne instability under the PCC condition. Compound **17** was rather unstable. After its purification on a silica gel column, **17** was immediately cross-coupled with 3-bromofuran in the presence of tetrakis(triphenylphosphine)palladium(0), copper(I) iodide, and diethylamine to furnish furan **18**.[16]

Scheme 3



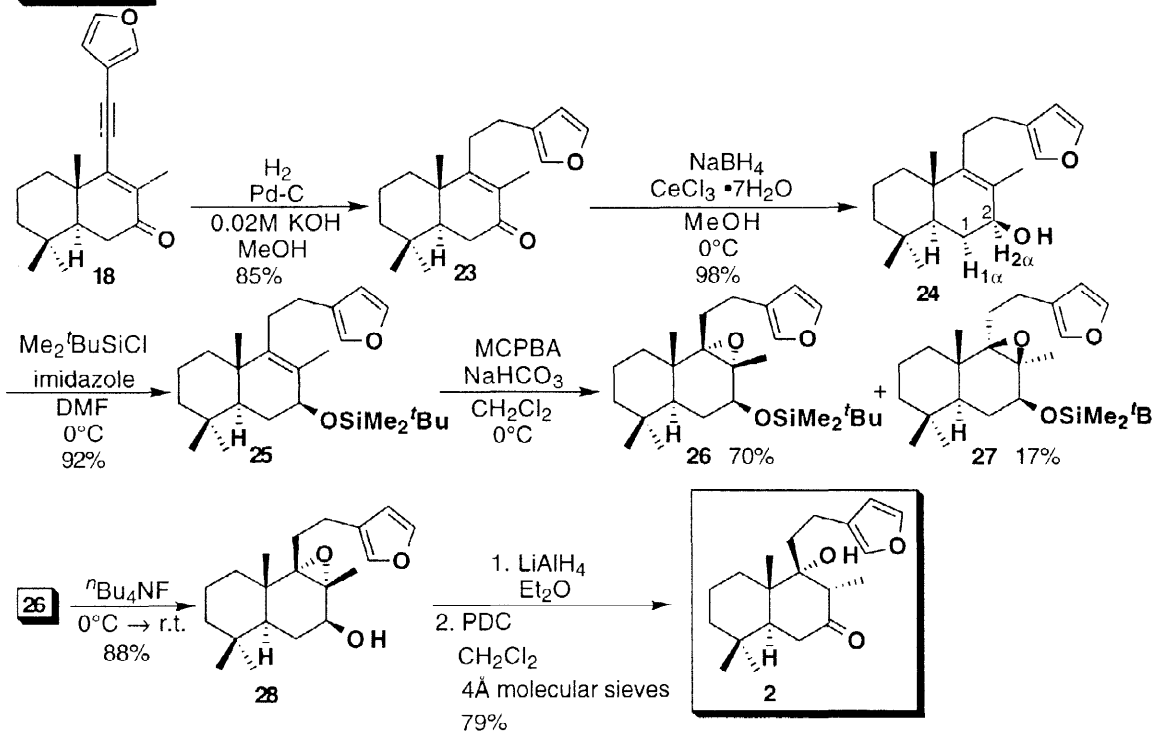
Another route in which **18** could be constructed was by elaboration from enone **14**. As outlined in Scheme 3, 1,2-addition of lithium acetylide tetramethylethylenediamine complex to **14** in diethyl ether at between -78°C and room temperature gave the tertiary alcohol **19**. For a similar reason as mentioned for the C_1-stereochemistry of **15** (*vide supra*), an α-alkynyl substitution pattern was again tentatively assigned to **19**. Silylation of **19** with a mixture of trimethylsilyl chloride and *N*,*N*-dimethylaminopyridine (DMAP) in triethylamine at room temperature afforded the silyl ether **20**. Again, a palladium(0)-catalyzed cross-coupling Sonogashira reaction between 3-bromofuran and **20** was performed,[16] producing furan **21**. After desilylation of **21** with tetrabutylammonium fluoride in tetrahydrofuran at 0°C, the resulting tertiary alcohol **22** was allowed to undergo a similar 1,3-transposition with subsequent oxidation in the presence of PCC and 4Å molecular sieves at room temperature to give **18**.[15] In this manner, the preparation of the desired unsaturated ketone **18** was achieved in five steps from **14** with an overall yield of 58%. Despite the stereochemistry at C_1 is inconsequential for compounds **19**, **20**, **21** and **22**, it is noteworthy that these compounds should all be of 1*S*-configuration. The synthetic pathway as described in Scheme 2 was eventually engaged in our synthesis of hispanolone (**2**) because of its relatively higher overall yield (65%).

With the unsaturated ketone **18** in hand, the remaining steps towards the total synthesis of hispanolone (**2**) are shown in Scheme 4. Thus, the room temperature hydrogenation of **18** in the presence of 10% palladium on charcoal and potassium hydroxide in methanol[17] led to enone **23**. However, it was uncovered that the percentage yield of enone **23** varied when the hydrogenation conditions were not monitored carefully, different

amounts of KOH or 10% Pd-C being considered to be crucial factors. After much experimentation, the use of 0.02N KOH was found to be optimal. Noteworthy is that enone **23** is a known molecule obtained previously by way of dehydration of the naturally occurring hispanolone (**2**).[4] The structure of **23** was therefore confirmed by comparison of its ^{1}H NMR, ^{13}C NMR and mass spectra with those reported in the literature.[2]

The Weitz-Scheffer epoxidation[18] of **23** was attempted. However, we were unable to epoxidize the enone **23** in a trivial manner, presumably due to the steric hindrance of the tetrasubstituted alkene. Another entry was finally designed to epoxidize **23** through the use of an electrophilic epoxidizing agent. This strategy is depicted in Scheme 4. First, the carbonyl group of enone **23** was reduced by sodium borohydride with the assistance of cerium(III) chloride heptahydrate in methanol[19] at 0°C to afford the allylic alcohol **24**, whose hydroxyl group should be β due to the appearance of a triplet for H-2 at δ 4.10 (J = 8.1 Hz) in its ^{1}H NMR spectrum, the reason being the distorted bicyclic chair form of **24**. As such, through the C_1-C_2 axis in **24**, it can be observed that the two dihedral angles, namely $\phi(H_{2\alpha}\text{-C-C-H}_{1\beta})$ and $\phi(H_{2\alpha}\text{-C-C-H}_{1\alpha})$ were in a position resulting in two relatively large coupling constants for $H_{2\alpha}$. These two coupling constants were close in magnitude so that a triplet at δ 4.10 with J = 8.1 Hz was detected on the ^{1}H NMR spectrum of **24**. In contrast, the corresponding stereomer with an α-hydroxyl group should display a doublet or a doublet of doublets in its proton NMR spectrum, presumably due to a small dihedral angle $\phi(H_{2\beta}\text{-C-C-H}_{1\beta})$ accompanying a nearly 90° dihedral angle $\phi(H_{2\beta}\text{-C-C-H}_{1\alpha})$.

Scheme 4



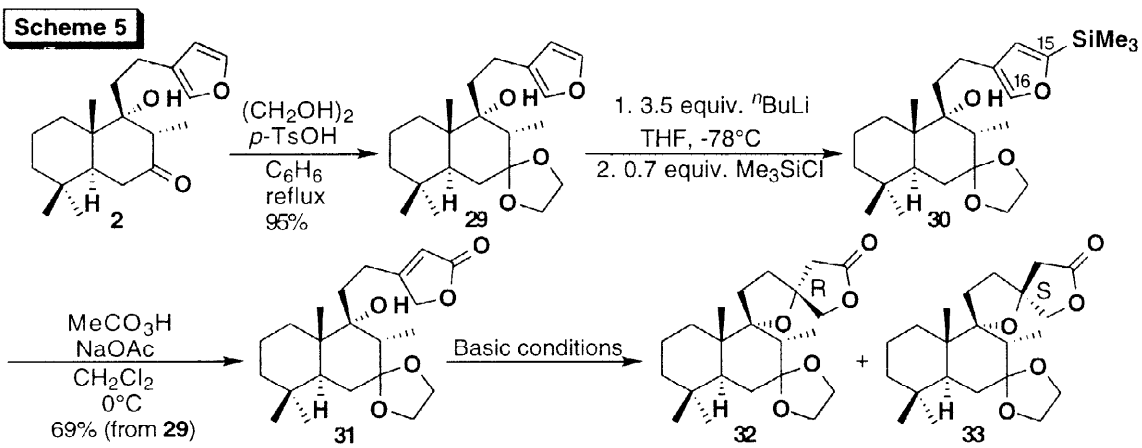
The hydroxyl group of **24** was then protected as a silyl ether by treatment with *tert*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethyl formamide, furnishing compound **25**. The alkene moiety in silyl ether **25** was successfully epoxidized on action with *m*-chloroperoxybenzoic acid under buffered condition,[20] leading to a chromatographically separable mixture of a pair of diastereomers, the desired α-epoxide **26** and the undesired β-epoxide **27** in a molar ratio of 4:1. Desilylation of **26** with tetrabutylammonium fluoride in tetrahydrofuran at

between 0°C and room temperature gave the α-epoxy alcohol **28** that was a known compound obtained previously by sequential transformations from the naturally occurring hispanolone (**2**).[2a] Finally, the epoxy moiety in **28** was reduced with lithium aluminum hydride[21] in diethyl ether at room temperature to afford a diol, which was not purified further because of its instability during silica gel column chromatography, and was immediately oxidized under neutral reaction condition by utilizing PDC and 4Å molecular sieves in dichloromethane to furnish our desired target molecule hispanolone (**2**). The physical and spectroscopic data of the synthetic **2** are in full agreement with those of the naturally occurring hispanolone (**2**).[2,5]

With now at our disposal a sufficient amount of synthetic **2**, we attempted to improve on our own synthesis of prehispanolone (**3**) which was accomplished recently employing naturally occurring hispanolone (**2**) as precursor.[10] In this literature synthesis, the deprotonation-silylation of furan **29** was found to provide an inseparable mixture of 15-trimethylsilylfuran **30** as well as its regioisomer, 16-trimethylsilylfuran, whose yields as determined by ^{1}H NMR spectroscopy were 55% and 27%, respectively. In order to improve the yield of **30** and to decrease the formation of the undesired regioisomer, we would like to search for a remedy in which C-15 deprotonation and silylation were predominant.

As depicted in Scheme 5, the keto group of **2** was first protected as acetonide **29**. Compound **29** was then treated with 3.5 equivalents of *n*-BuLi in THF at -78°C for 45 minutes and then 0.7 equivalents of trimethylsilyl chloride was added.[22] The resulting silylation product was purified through a silica gel column, and the product **30** was not characterized further and was oxidized immediately at 0°C with peroxyacetic acid under buffered conditions[23] to furnish butenolide **31** 69% overall yield from **29**. The spectroscopic data of the synthetic **31** are in full agreement with those of the previously prepared **31**.[10] A Comparison of this new procedure with the original one (25%, 4 steps, **2** to **31**)[10] revealed that the aforementioned new strategy only required 3 steps (overall yield 66%) in the conversion of **2** to **31**. Furthermore, this new route also provided a chromatographically separable **30** whose purity was satisfactory for spectroscopic identifications and subsequent reactions.

Scheme 5



Our next attempt was to improve the stereochemistry in the cyclization of **31** through the base induced intramolecular Michael addition. However, we were unable to provide a satisfactory result, despite a number of bases in achiral and chiral forms being tried. These bases included triethylamine, (-)-sparteine, 1-adamantanamine, and (*R*)-(+)-*N*,*N*-dimethyl-1-phenethylamine. Other chiral bases[24] and several amino acids,

i.e., (*S*)-proline, (*S*)-lysine, and (*R*)-arginine were tested as well. Likewise, these bases did not catalyze the formation of *R*-isomer **32** in a stereoselective manner. Use of cesium carbonate was found to merely cause decomposition of the starting material even at room temperature. Finally, cyclization of **31** was only achieved with two equivalents of DBU in refluxing triethylamine, yielding a chromatographically separable mixture of a pair of the known diastereomers **32** and **33** in a molar ratio of 1:1.[10b]

Conclusion

We have established a synthetic strategy to achieve the first total synthesis of hispanolone (**2**) from the commercially available (*S*)-(+)-Wieland-Miescher ketone (**1**). The spectroscopic and physical data of the synthetic hispanolone are in full agreement with those of the naturally occurring **2**. Experimentally, this synthetic program took 20 steps in 11% overall yield, starting from **1**. It is worth noting that the yields and steps as depicted in Scheme 2 were employed to calculate the total number of steps and overall yield. In addition to the total synthesis of **2**, partial improvements of the literature synthesis of prehispanolone (**3**) have also been attained. The stereoselective intramolecular Michael cyclization of **31**, as induced by bases, was found to be unsuccessful in affording the *R*-isomer **32** in a better ratio.

Experimental Section

(+)-(4a*S*, 5*S*)-4,4a,5,6,7,8-Hexahydro-5-hydroxy-4a-methylnaphthalen-2(3*H*)-one (5).[12] To a stirred solution of enone **1** (15.7 g, 90 mmol) in EtOH (333 mL) at 0°C was added portionwise $NaBH_4$ (1.1 g, 30 mmol) and then the mixture was stirred for 2 minutes at 0°C. The mixture was treated with HOAc (10 mL) and stirred for another 5 minutes at 0°C. After evaporating the solvent, the residue was partitioned between CH_2Cl_2 (250 mL) and sat. aq. NaCl (250 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on a silica gel column (1.4 kg, hexanes-EtOAc 1:1) to afford alcohol **5** (15.1 g, 95%) as a yellow oil: $[\alpha]_D^{25}$ +122.9 (*c* 0.34, $CHCl_3$) {lit[12a] $[\alpha]_D^{15}$ +122.2 (*c* 0.18, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 3H), 1.16-2.22 (m, 10H), 3.19 (dd, *J* = 1.4, 4.2 Hz, 1H), 3.94 (br s, 1H), 5.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.86, 22.70, 29.51, 31.63, 33.15, 33.59, 41.28, 77.19, 124.43, 169.81, 200.10; MS *m/z* 180 (M^+).

(+)-(4a*S*, 5*S*)-5-Benzoyl-4,4a,5,6,7,8-hexahydro-4a-methylnaphthalen-2(3*H*)-one (6).[12] To a solution of alcohol **5** (18.3 g, 0.1 mol) in pyridine (8.7 mL, 0.1 mol) at 0°C was added benzoyl chloride (12 mL, 0.1 mol) and the resulting mixture was stirred for 10 hours at room temperature. After filtration, the filtrate was diluted with H_2O (190 mL) and then extracted with Et_2O (3X200 mL). The extract was washed with H_2O (2X150 mL), dried over $MgSO_4$, and evaporated to give a residue, which was purified by column chromatography on silica gel (2.3 kg, hexanes-EtOAc 5:1) to provide benzoate **6** (27.8 g, 96%) as a yellow oil: $[\alpha]_D^{25}$ +159.3 (*c* 0.41, $CHCl_3$) {lit[12a] $[\alpha]_D^{15}$ +158.9 (*c* 0.18, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.53-2.39 (m, 10H), 4.85 (dd, *J* = 4.4, 11.5 Hz, 1H), 5.79 (s, 1H), 7.38-7.43 (m, 2H), 7.50-7.55 (m, 1H), 7.98-8.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.66, 22.70, 26.69, 31.55, 33.23, 33.85, 40.51, 79.52, 152.57, 128.26, 129.32, 129.87, 132.97, 165.48, 166.62, 198.79; MS *m/z* 284 (M^+).

(+)-(4a*S*, 5*S*)-5-Benzoyloxy-3,4,4a,5,6,7-hexahydro-1,1,4a-trimethylnaphthalen-2(1*H*)-one (7)[12] To a stirred solution of freshly sublimed *t*-BuOK (0.4 g, 3 mmol) in *t*-BuOH (2 mL) was added a solution of enone **6** (0.3 g, 1 mmol) in *t*-BuOH (5 mL) and the resulting mixture was stirred for 15 minutes at room temperature. After that MeI (0.3 mL, 4 mmol) was added and the resulting mixture was further stirred for 45

minutes at room temperature and was then neutralized at 0°C by careful addition of 10% HCl. The mixture was extracted with Et_2O (3X20 mL) and the extract was washed with sat. aq. NaCl (2X15 mL), and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel (40 g, hexanes-EtOAc 100:3) to afford compound **7** (0.3 g, 84%) as a yellow oil: $[\alpha]_D^{25}$ +22.2 (*c* 0.37, $CHCl_3$) {lit[12a] $[\alpha]_D^{15}$ +22.4 (*c* 0.17, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 3H), 1.27 (s, 3H), 1.29 (s, 3H), 1.59-2.55 (m, 8H), 5.05 (dd, *J* = 4.9, 11.3 Hz, 1H), 5.61 (t, *J* = 3.8 Hz, 1H), 7.42-7.49 (m, 2H), 7.54-7.58 (m, 1H), 8.03-8.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.01, 22.89, 24.19, 27.08, 29.27, 30.88, 33.41, 38.34, 48.56, 78.28, 120.41, 128.31, 129.42, 130.31, 132.90, 147.21, 166.00, 215.15; MS *m/z* 312 (M^+).

(-)-(1*S*, 8a*S*)-1,2,3,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphth-1-ol (8).[12] A mixture of ketone **7** (1.8 g, 6 mmol), KOH (3.0 g, 50 mmol), and $N_2H_4 \cdot H_2O$ (3.3 mL, 0.07 mol) in diethylene glycol (33 mL) was refluxed for 2 hours and then the excess of $N_2H_4 \cdot H_2O$ was evaporated. The reaction mixture was further refluxed for 4 hours, diluted with H_2O (100 mL), and then extracted with Et_2O (3X110 mL). The extract was dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column (140 g, hexanes-EtOAc 5:1). The product was recrystallized from hexanes to provide alcohol **8** (1.0 g, 93%) as white needle-shaped crystals: m.p. 82-83°C (lit[12a] m.p. 82-83°C); $[\alpha]_D^{25}$ -58.2 (*c* 0.29, $CHCl_3$) {lit[12a] $[\alpha]_D^{15}$ -58.8 (*c* 0.16, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3H), 1.12 (s, 6H), 1.13-2.16 (m, 10H), 3.44 (dd, *J* = 5.4, 10.3 Hz, 1H), 5.42 (t, *J* = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.12, 19.47, 24.64, 26.03, 30.30, 32.25, 35.20, 37.59, 39.11, 41.06, 78.12, 117.68, 148.70; MS *m/z* 194 (M^+).

(-)-(1*S*, 4a*S*, 8a*S*)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5,5,8a-trimethylnaphth-1-ol (9).[12] A mixture of alkene **8** (0.82 g, 0.4 mmol) and Adams' catalyst (0.12 g) in HOAc (10 mL) was stirred under an atmosphere of H_2 until absorption of which ceased. After filtration, H_2O (20 mL) was added and the resulting mixture was extracted with Et_2O (3X30 mL). The extract was washed with sat. aq. $NaHCO_3$ (3X60 mL) until neutral, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (100 g, hexanes-EtOAc 10:1). The crude product was recrystallized from hexanes to give alcohol **9** (0.8 g, 95%) as white needle-shaped crystals: m.p. 87-88°C (lit[12a] m.p. 88-89°C); $[\alpha]_D^{25}$ -1.3 (*c* 0.35, $CHCl_3$) {lit[12a] $[\alpha]_D^{17}$ -1.5 (*c* 0.40, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 0.81 (s, 3H), 0.83 (s, 3H), 0.86 (s, 3H)), 0.89-1.74 (m, 13H), 3.11 (dd, *J* = 4.4, 11.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.01, 18.32, 20.86, 21.74, 24.49, 30.09, 32.80, 33.27, 37.50, 39.42, 42.08, 52.28, 80.73; MS *m/z* 196 (M^+).

(-)-(4a*S*, 8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphthalen-1(2*H*)-one (10).[12] To a mixture of alcohol **9** (0.79 g, 4 mmol) in CH_2Cl_2 (20 mL) were added Florisil (1.3 g) and PCC (1.3 g, 6 mmol). The resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was then diluted with Et_2O (120 mL) and filtered through a pad of celite. The filtrate was evaporated to give a residue, which was subjected to silica gel column chromatography (100 g, hexanes-EtOAc 20:1) to yield ketone **10** (0.7 g, 90%) as a colorless oil: $[\alpha]_D^{20}$ -40.1 (*c* 0.15, $CHCl_3$) {lit[12a] $[\alpha]_D^{17}$ -39.1 (*c* 0.44, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H), 0.90 (s, 3H), 1.12 (s, 3H), 1.23-2.63 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 17.98, 18.47, 20.84, 21.96, 26.23, 32.94, 33.02, 34.03, 37.50, 41.48, 48.95, 53.37, 215.80; MS *m/z* 194 (M^+).

(+)-(4a*S*, 8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-1-trimethylsiloxynaphthalene (11). To a stirred solution of *i*-Pr_2NH (7.2 mL, 50 mmol) in anhydrous THF (30 mL) was added dropwise 1.6 M *n*-BuLi in hexane (30.6 mL, 50 mmol) over 8 minutes at 0°C and then the mixture was further stirred for 20 minutes. The above prepared LDA solution was injected to a stirred solution of ketone **10** (9.50 g, 50 mmol) in

anhydrous THF (110 mL) at 0°C and then the resulting mixture was stirred for 45 minutes. After an injection of Me_3SiCl (6.8 mL, 50 mmol) at 0°C, the reaction mixture was warmed to room temperature and stirred for 50 minutes. 0.5 M aq. $NaHCO_3$ (30 mL) was added and the organic phase was separated. The aq. phase was extracted with Et_2O (3X40 mL) and the combined organic layer was dried over $MgSO_4$. After evaporation, the residue was purified on a silica gel column (1.5 kg, hexanes) to afford the enol silyl ether **11** (10.8 g, 83%) as a colorless oil: $[\alpha]_D^{25}$ +63.8 (*c* 1.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.17 (s, 9H), 0.85 (s, 3H), 0.89 (s, 3H), 1.05 (s, 3H), 1.11-2.02 (m, 11H), 4.53 (t, *J* = 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 0.41, 18.66, 18.86, 19.69, 21.66, 24.48, 33.13, 33.26, 35.39, 39.29, 42.04, 51.71, 99.56, 158.91; MS *m/z* 266 (M^+); HRMS (M^+) *m/z* calcd. for $C_{16}H_{30}OSi$: 266.2066. Found: 266.2066.

(4a*S*, 8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethylnaphthalen-1(2*H*)-one (12). A mixture of $PhCH_2Me_3NF$ (0.3 g; 2 mmol) (pre-dried under vacuum at 60°C for 24 hours) and 4Å molecular sieves (1 g) was suspended in THF (10 mL). The mixture was stirred for 20 hours at room temperature. MeI (0.3 mL, 5 mmol) and a solution of the enol silyl ether **11** (0.42 g, 2 mmol) in THF (3 mL) was added successively to the suspension at room temperature. The resulting reaction mixture was stirred for 30 minutes. The suspension was filtered and washed with Et_2O (3X7 mL). After evaporation, the residue was purified on a silica gel column (45 g, hexanes-EtOAc 100:1) to furnish a diastereomeric mixture of α-methyl ketone **12** (0.3 g, 94%) as a pale yellow oil, as well as the recovered ketone **10** (10 mg, 2%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.78-1.04 (m, 15H), 1.42-2.00 (m, 8H), 2.41-2.59 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.86, 15.85, 17.59, 18.04, 18.56, 18.72, 21.15, 21.42, 21.83, 26.50, 32.48, 32.88, 33.03, 34.70, 35.56, 39.31, 39.67, 41.42, 41.70, 46.64, 47.22, 54.01, 216.35, 220.05; MS *m/z* 208 (M^+); HRMS (MH^+) *m/z* calcd. for $C_{14}H_{25}O$: 209.1905. Found: 209.1887.

(4a*S*, 8a*S*)-2-Bromo-3,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalen-1(2*H*)-one (13). To a stirred solution of ketone **12** (0.2 g, 0.9 mmol) in HOAc (13 mL) was added pyridinium bromide perbromide (0.3 g, 0.9 mmol). The mixture was then stirred for 2 hours at room temperature. After addition of H_2O (28 mL), the resulting mixture was extracted with Et_2O (3X50 mL). The extract was washed with sat. aq. $NaHCO_3$ (2X60 mL), dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (35 g, hexanes-EtOAc 50:1) to yield a diastereomeric mixture of bromide **13** (0.25 g, 97%) as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 0.91 (s, 3H), 1.04 (s, 3H), 1.06-1.79 (m, 7H), 1.80 (s, 3H), 1.83-2.25 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 17.37, 17.82, 17.98, 18.95, 21.24, 21.86, 23.36, 29.77, 30.30, 32.07, 32.86, 33.98, 34.04, 34.63, 35.36, 35.57, 40.95, 41.33, 43.71, 44.74, 46.63, 49.21, 53.15, 60.47, 61.08, 197.44, 198.32; MS *m/z* 288 (MH^+); Anal. Calcd. for $C_{14}H_{23}BrO$: C, 58.54; H, 8.07. Found: C, 58.61; H, 8.42.

(-)-(4a*S*, 8a*S*)-4,4a,5,6,7,8-Hexahydro-2,5,5,8a-tetramethylnaphthalen-1(8a*H*)-one (14). A mixture of bromide **13** (3.5 g, 10 mmol) and DBU (2.2 mL, 10 mmol) in toluene (60 mL) was refluxed for 2 hours. The mixture was diluted with Et_2O (320 mL), washed successively with H_2O (130 mL), 10% HCl (130 mL), and brine (2X170 mL), and dried over $MgSO_4$. After evaporation, the residue was chromatographed through a silica gel column (350 g, hexanes-EtOAc 10:1) to afford enone **14** (2.3 g, 94%) as white needle-shaped crystals: m.p. 75-77°C; $[\alpha]_D^{25}$ -81.3 (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (s, 3H), 0.98 (s, 3H), 1.03 (s, 3H), 1.15-1.62 (m, 5H), 1.74 (s, 3H), 1.19-2.36 (s, 4H), 6.66 (t, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.97, 16.69, 17.78, 21.78, 23.96, 31.90, 32.86, 33.14, 41.19, 44.60, 48.96, 132.42, 142.72, 202.23; MS *m/z* 206 (M^+); Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.55; H, 10.61.

(-)-(1*R*, 4a*S*, 8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-trimethylsilylethynylnaphth-1-ol (15). To a stirred solution of trimethylsilylacetylene (0.3 mL, 2 mmol) in anhydrous Et_2O (5 mL) was added 1.6 M *n*-BuLi in hexane (1.4 mL, 2 mmol) at 0°C and then the mixture was stirred further for 20 minutes. The above prepared solution was injected into a solution of enone **14** (250 mg, 2 mmol) in Et_2O (256 mL) at -78°C and the resulting mixture was warmed to room temperature after 5 minutes. H_2O (30 mL) was added to the mixture and the aq. layer was extracted with Et_2O (3X30 mL). The extract was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on a silica gel column (35 g, hexanes-EtOAc 20:1) to yield alcohol **15** (240 mg, 98%) as a pale yellow oil: $[\alpha]_D^{25}$ -221.2 (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.16 (s, 9H), 0.87 (s, 3H), 0.91 (s, 3H), 0.93 (s, 3H), 1.09-1.63 (m, 6H), 1.78 (s, 3H), 1.79-2.07 (m, 4H), 5.42 (t, *J* = 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ -0.05, 13.50, 17.98, 18.46, 21.65, 23.95, 32.76, 32.90, 33.44, 41.30, 42.00, 45.01, 77.69, 90.15, 108.92, 123.51, 135.18; MS *m/z* 304 (M^+); HRMS (M^+) *m/z* calcd. for $C_{19}H_{32}OSi$: 304.2222. Found: 304.2206; Anal. Calcd. for $C_{19}H_{32}OSi$: C, 74.93; H, 10.59. Found; C, 75.05; H, 10.90.

(+)-(4a*S*, 8a*S*)-4a,5,6,7,8,8a-Hexahydro-3,4a,8,8-tetramethyl-4-trimethylsilylethynylnapthalen-2(1*H*)-one (16). A mixture of alcohol **15** (550 mg, 2 mmol), 4Å molecular sieves (1.2 g), and pyridinium chlorochromate (1.2 g, 5 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 2 hours. The reaction mixture was diluted with Et_2O (200 mL) and filtered through a pad of celite. The filtrate was dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column (65 g, hexanes-EtOAc 20:1) to provide compound **16** (0.45 g, 82%) as white needle-shaped crystals: m.p. 57-59°C; $[\alpha]_D^{25}$ +81.3 (*c* 1.09, $CHCl_3$): ^1H NMR ($CDCl_3$) δ 0.22 (s, 9H), 0.87 (s, 3H), 0.90 (s, 3H), 1.16 (s, 3H), 1.19-1.71 (m, 6H), 1.91 (s, 3H), 2-2.54 (m, 3H); ^{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; MS *m/z* 302 (M^+); Anal. Calcd. for $C_{19}H_{30}OSi$: C, 75.43; H, 10.00. Found: C, 75.39; H, 10.26.

(+)-(4a*S*, 8a*S*)-4-Ethynyl-4a,5,6,7,8,8a-hexahydro-3,4a,8,8-tetramethyl-naphthalen-2(1*H*)-one (17). To a stirred solution of compound **16** (270 mg, 0.9 mmol) in THF (4 mL) was added 1 M *n*-Bu_4NF in THF (1.1 mL, 1 mmol) at 0°C and the reaction mixture was stirred for a further 30 minutes. After evaporation, the residue was chromatographed on silica gel (30 g, hexanes-EtOAc 20:1) to furnish **17** (210 mg, 99%) as a colorless oil: $[\alpha]_D^{25}$ +73.5 (*c* 0.97, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (s, 3H), 0.91 (s, 3H), 1.17 (s, 3H), 1.20 (m, 5H), 1.93 (s, 3H), 1.95-2.57 (m, 4H), 3.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.92, 18.48, 20.91, 32.13, 32.91, 35.09, 37.36, 39.02, 40.95, 49.87, 79.60, 92.80, 138.06, 148.49, 199.09; MS *m/z* 230 (M^+); HRMS (M^+) *m/z* calcd. for $C_{16}H_{22}O$: 230.1671. Found: 230.1680.

(+)-(4a*S*, 8a*S*)-4-(3-Furyl)ethynyl-4a,5,6,7,8,8a-hexahydro-3,4a,8,8-tetramethylnaphthalen-2(1*H*)-one (18).

(a) From **17**: A mixture of compound **17** (0.7 g, 3 mmol), $Pd(PPh_3)_4$ (0.2 g, 0.2 mmol), CuI (20 mg, 0.2 mmol), and 3-bromofuran (1.6 g, 10 mmol) in Et_2NH (500 mL) was refluxed for 2 hours. After evaporation, the residue was purified on a silica gel column (100 g, hexanes-EtOAc 40:1) to afford compound **18** (0.7 g, 82%) as white needle-shaped crystals: m.p. 94-96°C; $[\alpha]_D^{25}$ +119.6 (*c* 1.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (s, 3H), 0.93 (s, 3H), 1.21 (s, 3H), 1.24-1.78 (m, 6H), 1.97 (s, 3H), 2.07-2.58 (m, 3H), 6.49 (m, 1H), 7.42 (m, 1H), 7.69 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.19, 18.74, 19.06, 21.11, 32.32, 33.15, 35.34, 37.73, 39.55, 41.17, 50.10, 87.96, 96.69, 107.40, 112.33, 136.21, 143.23, 145.95, 150.02, 199.55; HRMS (MH^+)*m/z* calcd. for

$C_{20}H_{25}O_2$: 297.1849. Found: 297.1851; Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.56; H, 8.31. The dimer (20 mg, 2%) was also obtained as yellow needle-shaped crystals: m.p. 253-255°C; ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 6H), 0.90 (s, 6H), 1.19 (s, 6H), 1.21-1.80 (m, 12H), 1.95 (s, 6H), 2.01-2.57 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 14.44, 18.58, 19.23, 21.02, 32.24, 33.13, 35.23, 37.59, 39.85, 41.01, 50.03, 82.64, 87.91, 144.00, 148.09, 199.04; MS *m/z* 458 (M^+); Anal. Calcd. for $C_{32}H_{42}O_2$: C, 83.79; H, 9.23. Found: C, 83.77; H, 9.50.

(b) From **22**: A mixture of compound **22** (33 mg, 0.1 mmol), pyridinium chlorochromate (71 mg, 0.3 mmol), and molecular sieves (70 mg) in CH_2Cl_2 (4 mL) was stirred for 58 hours at room temperature. The reaction mixture was diluted with Et_2O (20 mL) and filtered through a pad of celite. The filtrate was dried over $MgSO_4$ and evaporated to give a residue, which was purified on silica gel column chromatography (5 g, hexanes-EtOAc 10:1) to provide compound **18** (25 mg, 78%) as white needle-shaped crystals: m.p. 94-96°C; the spectroscopic data are identical to those reported previously.

(-)-(1*S*, 4a*S*, 8a*S*)-1-Ethynyl-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphth-1-ol (19). To a stirred solution of enone **14** (50 mg, 0.2 mmol) in anhydrous Et_2O (30 mL) was added lithium acetylide tetramethylethylenediamine complex (50 mg, 0.3 mmol) at -78°C and then the reaction mixture was warmed to room temperature. After additional stirring for 5 minutes at room temperature, H_2O (7 mL) was added and the aqueous layer was extracted with Et_2O (3X9 mL). The extract was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (9 g, hexanes-EtOAc 20:1) to give alcohol **19** (56 mg, 99%) as a pale yellow oil: $[\alpha]_D^{25}$ -217.6 (*c* 1.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 3H), 0.91 (s, 3H), 0.94 (s, 3H), 1.01-1.76 (m, 6H), 1.18 (s, 3H), 1.88-2.01 (m, 4H), 2.57 (s, 1H), 5.44 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.07, 17.48, 18.08, 21.42, 23.57, 32.46, 33.08, 40.74, 41.42, 44.48, 74.17, 76.21, 86.34, 123.46, 134.75; MS *m/z* 323 (M^+); Anal. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.76; H, 10.68.

(-)-(1*S*, 4a*S*, 8a*S*)-1-Ethynyl-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-trimethylsiloxynaphthalene (20). To a stirred solution of **19** (0.14 g, 0.6 mmol) and *N,N*-dimethylaminopyridine (220 mg, 2 mmol) in THF (8 mL) was added Me_3SiCl (0.2 mL, 1 mmol) at room temperature and the resulting mixture was then stirred for 21 hours. After that sat. aq. $NaHCO_3$ (6 mL) was added. The mixture was extracted with Et_2O (3X7 mL) and dried over $MgSO_4$. After evaporation, the residue was chromatographed on a silica gel column (30 g, hexanes) to afford compound **20** (180 mg, 98%) as white solids: m.p. 88-90°C; $[\alpha]_D^{25}$ -133.5 (*c* 1.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H), 088 (s, 3H), 0.90 (s, 3H), 0.92 (s, 3H), 1.21-1.59 (m, 6H), 1.75 (s, 3H), 1.80-2.03 (m, 3H), 2.60 (s, 1H), 5.39 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 2.37, 13.57, 18.62, 19.36, 21.76, 24.00, 32.78, 32.78, 34.32, 41.83, 42.14, 44.51, 75.97, 79.10, 86.58, 122.73, 137.01; MS *m/z* 304 (M^+); Anal. Calcd. for $C_{19}H_{32}OSi$: C, 74.93; H, 10.59. Found: C, 74.98; H, 10.92.

(-)-(1*S*, 4a*S*, 8a*S*)-1-(3-Furyl)ethynyl-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-trimethylsiloxynaphthalene (21). A mixture of **20** (180 mg, 0.6 mmol), $Pd(PPh_3)_4$ (30 mg, 0.03 mmol), CuI (10 mg, 0.06 mmol), and 3-bromofuran (260 mg, 2 mmol) in Et_2NH (120 mL) was refluxed for 12 hours. After evaporation, the residue was purified on a silica gel column (25 g, hexanes) to afford compound **21** (180 mg, 80%) as white needle-shaped crystals: m.p. 30-32°C; $[\alpha]_D^{25}$ -196.4 (*c* 2.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H), 0.88 (s, 3H), 0.93 (s, 6H), 1.06-1.73 (m, 6H), 1.77 (s, 3H), 1.86-2.06 (m, 3H), 5.40 (s, 1H), 6.43 (s, 1H), 7.37 (s, 1H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 2.28, 13.72, 18.67, 19.56, 21.80, 24.09,

32.92, 34.56, 41.99, 42.48, 44.83, 78.76, 79.70, 94.00, 107.58, 112.37, 122.58, 136.86, 142.72, 145.07; MS *m/z* 370 (M^+); Anal. Calcd. for $C_{23}H_{34}O_2Si$: C, 74.54; H, 9.25. Found: C, 74.42; H, 9.48.

(-)-(1*S*, 4a*S*, 8a*S*)-1-(3-Furyl)ethynyl-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphth-1-ol (22). To a stirred solution of compound **21** (15 mg, 0.04 mmol) in THF (2 mL) was added 1 M *n*-Bu_4NF in THF (0.1 mL, 0.07 mmol) at 0°C and then the mixture was stirred for 20 minutes. After that the solvent was evaporated and the residue was chromatographed on a silica gel column (3 g, hexanes-EtOAc 20:1) to provide compound **22** (13 mg, 98%) as white needle-shaped crystals: m.p. 75-76°C; $[\alpha]_D^{25}$ -282.8 (*c* 3.12, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (s, 3H), 0.93 (s, 3H), 0.99 (s, 3H), 1.20-1.81 (m, 6H), 1.84 (s, 3H), 1.85-2.04 (m, 3H), 5.47 (m, 1H), 6.43 (d, *J* = 1.6 Hz, 1H), 7.36 (t, *J* = 1.6 Hz, 1H), 7.59 (d, *J* = 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.58, 18.04, 18.46, 21.76, 23.97, 32.87, 33.76, 41.49, 41.88, 45.23, 77.49, 77.97, 93.68, 107.24, 112.60, 123.61, 135.05, 142.63, 145.40; MS *m/z* 298 (M^+); Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.50; H, 9.01.

(+)-(4a*S*, 8a*S*)-4-[2-(3-Furyl)ethyl]-4a,5,6,7,8,8a-hexahydro-3,4a,8,8-tetramethylnaphthalen-2(1*H*)-one (23).[2] A mixture of compound **18** (20 mg, 0.07 mmol) and 10% Pd-C (0.03 g) in 0.02 N KOH in MeOH (3 mL) was stirred under H_2 for 7 minutes. The reaction mixture was filtered and evaporated to give a residue, which was chromatographed on a silica gel column (4 g, hexanes-EtOAc 20:1) to afford compound **23** (17 mg, 85%) as white needle-shaped crystals: m.p. 57-58°C (lit[2a] m.p. 58-60°C); $[\alpha]_D^{25}$ +40.8 (*c* 2.80, $CHCl_3$) {lit[2a] $[\alpha]_D^{20}$ +39.7 (*c* 1.12, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 0.89 (s, 3H), 0.92 (s, 3H), 1.08 (s, 3H), 1.2-1.77 (m, 7H), 1.78 (s, 3H), 2.0-2.55 (m, 6H), 6.31 (s, 1H), 7.26 (d, *J* = 0.9 Hz , 1H), 7.37 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 11.46, 18.12, 18.59, 21.31, 24.20, 30.19, 32.51, 33.12, 35.24, 35.88, 40.89, 41.28, 50.27, 110.56, 124.48, 130.34, 138.61, 143.01, 167.04, 200.31; MS *m/z* 300 (M^+). The spectroscopic and physical data of synthetic enone **23** are in full agreement with those of the known compound.[2]

(+)-(2*S*, 4a*S*, 8a*S*)-4-[2-(3-Furyl)ethyl]-1,2,4a,5,6,7,8,8a-octahydro-3,4a,8,8-tetramethylnaphth-2-ol (24). To a stirred solution of compound **23** (350 mg, 1 mmol) and $CeCl_3 \cdot 7H_2O$ (470 mg, 1 mmol) in MeOH (18 mL) was added $NaBH_4$ (190 Mg, 5 mmol) at 0°C and the reaction mixture was stirred for 5 minutes. Brine (6 mL) was added and the mixture was extracted with EtOAc (3X10 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (48 g, hexanes-EtOAc 5:1) to provide compound **24** (340 mg, 98%) as a colorless oil: $[\alpha]_D^{25}$ +45.8 (*c* 3.76, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H), 0.90 (s, 3H), 1.03 (s, 3H), 1.17-1.61 (m, 9H), 1.73 (s, 3H), 1.78-2.50 (m, 4H), 4.10 (t, *J* = 8.1 Hz, 1H), 6.30 (s, 1H), 7.24 (s, 1H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.75, 18.82, 20.16, 21.16, 25.06, 28.92, 29.88, 32.94, 33.08, 36.88, 41.51, 49.87, 73.00, 110.75, 125, 129, 138.43, 142.73, 144; MS *m/z* 302 (M^+); HRMS (M^+) *m/z* calcd. for $C_{20}H_{30}O_2$: 302.2246. Found: 302.2232.

(+)-(2*S*, 4a*S*, 8a*S*)-2-*tert*-Butyldimethylsiloxy-4-[2-(3-furyl)ethyl]-1,2,4a,5,6,7,8,8a-octahydro-3,4a,8,8-tetramethylnaphthalene (25). To a stirred solution of compound **24** (530 mg, 2 mmol) and imidazole (320 mg, 5 mmol) in DMF (12 mL) was added *t*-$BuMe_2SiCl$ (370 mg, 2 mmol) at 0°C. After 5 minutes, the reaction was warmed to room temperature and stirred for 2 hours. To the mixture was added sat. aq. $NaHCO_3$ solution (10 mL), extracted with Et_2O (3x20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (96 g, hexanes) to afford compound **25** (670 mg, 92%) as a colorless oil: $[\alpha]_D^{25}$ +32.4 (*c* 3.63, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 3H), 0.91 (s, 3H), 0.93 (s, 9H), 1.03 (s, 3H), 1.15-1.52 (m, 8H), 2.25 (s, 3H), 1.9-2.49 (m, 5H), 4.12 (t, *J* = 8.3 Hz,

1H), 6.30 (s, 1H), 7.24 (s, 1H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -4.67, -3.98, 15.24, 18.24, 18.85, 20.02, 21.72, 25.16, 26.01, 29.044, 29.94, 32.86, 33.05, 36.96, 39.89, 41.58, 49.98, 73.84, 110.79, 125.47, 130.10, 138.41, 142.67, 142.75; MS *m/z* 416 (M^+); HRMS $(M-H)^+$ *m/z* calcd. for $C_{26}H_{43}O_2Si$: 415.3027. Found: 415.3025.

(+)-(2*S*, 3*R*, 4*S*, 4a*S*, 8a*S*)-2-*tert*-Butyldimethylsiloxy-3,4-epoxy-4-[2-(3-furyl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-3,4a,8,8-tetramethylnaphthalene (26). To a stirred solution of compound **25** (840 mg, 2 mmol) and $NaHCO_3$ (1.0 g, 10 mmol) in CH_2Cl_2 (30 mL) was added *m*-chloroperoxbenzoic acid (1.5 g, 6 mmol) at 0°C and then the resulting reaction was stirred for 12 hours. To the reaction mixture was added sat. aq. $Na_2S_2O_3$ solution (25 mL). The mixture was extracted with CH_2Cl_2 (3X25 mL), dried over $MgSO_4$, and evaporated. The residue was purified on a silica gel column (90 g, hexanes-EtOAc 100:1) to provide the α-epoxide **26** (420 mg, 70% based on 64% conversion) as a colorless oil: $[\alpha]_D^{25}$ +46.6 (*c* 1.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.82 (s, 3H), 0.84 (s, 3H), 0.91 (s, 9H), 1.06 (s, 3H), 1.07-1.23 (m, 2H), 1.24 (s, 3H), 1.25-2.40 (m, 11H), 3.84 (t, *J* = 9 Hz, 1H), 6.26 (d, *J* = 0.9 Hz, 1H), 7.20 (s, 1H), 7.34 (t, *J* = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ -5.02, -4.14, 17.32, 17.71, 18.01, 18.35, 21.53, 21.58, 25.86, 27.16, 29.33, 32.61, 33.43, 34.44, 38.68, 40.24, 41.29, 65.48, 70.68, 72.09, 110.89, 125.11, 138.50, 142.71; MS *m/z* 432 (M^+); HRMS (M^+) *m/z* calcd. for $C_{26}H_{44}O_3Si$: 432.3060. Found: 432.3046. The diastereomeric β-epoxide **27** (90 mg, 17%) was also obtained as a colorless oil: $[\alpha]_D^{25}$ +37.7 (c 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.80 (s, 3H), 0.84 (s, 3H), 0.93 (s, 9H), 1.10 (s, 3H), 1.11-1.36 (m, 5H), 1.37 (s, 3H), 1.38-2.61 (m, 8H), 3.73 (dd, *J* = 5.7, 10.5 Hz, 1H), 6.24 (s, 1H), 7.20 (s, 1H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -4.70, -3.92, 16.83, 16.98, 18.18, 19.64, 21.95, 22.21, 25.93, 26.53, 31.80, 32.92, 33.67, 37.26, 38.27, 41.25, 51.32, 67.37, 73.83, 76.22, 110.67, 125.11, 138.42, 142.80; MS *m/z* 432 (M^+); HRMS (M^+) *m/z* calcd. for $C_{26}H_{44}O_3Si$: 432.3060. Found: 432.3059.

(+)-(2*S*, 3*R*, 4*S*, 4a*S*, 8a*S*)-3,4-Epoxy-4-[2-(3-furyl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-3,4a,8,8-tetramethylnaphth-2-ol (28).[2a] To a stirred solution of compound **26** (430 mg, 1 mmol) in THF (15 mL) was added 1 M *n*-Bu_4NF in THF (2.5 mL, 2 mmol) at 0°C and then the mixture was stirred for 20 hours. After evaporating the solvent, the residue was chromatographed on silica gel (40 g, hexanes-EtOAc 5:1) to provide compound **28** (280 mg, 88%) as a colorless oil: $[\alpha]_D^{25}$ +52.4 (*c* 1.06, $CHCl_3$) {lit[2a] $[\alpha]_D^{19}$ +55.4 (*c* 0.37, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H), 0.86 (s, 3H), 1.07 (s, 3H), 1.08-1.31 (m, 3H), 1.34 (s, 3H), 1.35-2.41 (m, 10H), 3.90 (t, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 0.9 Hz, 1H), 7.21 (s, 1H), 7.34 (t, *J* = 1.5 Hz, 1H); ^{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; MS *m/z* 318 (M^+). The spectroscopic and physical data of synthetic **28** are in full agreement with those of the known compound.[2a]

(-)-(3*S*, 4*R*, 4a*S*, 8a*S*)-4-[2-(3-Furyl)ethyl]-3,4,4a,5,6,7,8,8a-octahydro-4-hydroxy-3,4a,8,8-tetramethylnaphthalen-2(1*H*)-one (2).[2,5] To a stirred solution of compound **28** (92 mg, 0.3 mmol) in THF (8 mL) was added $LiAlH_4$ (110 mg, 3 mmol) at room temperature and the resulting mixture was stirred for 1 hour. The reaction was quenched by adding brine (6 mL), extracted with EtOAc (3X6 mL), dried over $MgSO_4$ and evaporated to give a residue, which was oxidized without further purification with pyridinium dichromate (152 mg, 0.4 mmol) and 4Å molecular sieves (150 mg) in CH_2Cl_2 (8 mL) at room temperature. After stirred for 45 minutes, the reaction mixture was diluted with Et_2O (40 mL) and then filtered through a pad of celite. The filtrate was dried over $MgSO_4$ and evaporated. The resulting product was purified by silica gel column

chromatography (10 g, hexanes-EtOAc 20:1) to furnish hispanolone (**2**) (72 mg, 79%) as white needle-shaped crystals: m.p. 143-145°C (lit[5a] m.p. 145-146°C); $[\alpha]_D^{25}$ -18.3 (*c* 0.64, $CHCl_3$) {lit[5a] $[\alpha]_D^{22}$ -18.2 (*c* 1.00, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 0.88 (s, 3H), 0.90 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 3H), 1.20-2.49 (m, 13H), 2.74 (q, *J* = 6.6 Hz, 1H), 6.27 (d, *J* = 0.9 Hz, 1H), 7.23 (s, 1H), 3.60 (t, *J* = 1.5Hz, 1H); ^{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; MS *m/z* 318 (M^+). The spectroscopic and physical data of synthetic hispanolone (**2**) are in full agreement with those of the naturally occurring **2**.[2,5]

(+)-(3*S*, 4*R*, 4a*S*, 8a*S*)-3-(1,3-Dioxolan-2-yl)-1-[2-(3-furyl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-2,5,5,8a-tetramethylnaphth-1-ol (**29**).[10] A mixture of compound **2** (0.1 g, 0.3 mmol), ethylene glycol (0.2 mL, 3 mmol), and *p*-TsOH•H_2O (6 mg, 0.03 mmol) in (20 mL) was refluxed for 6 hours. The reaction mixture was washed with sat. aq. $NaHCO_3$ solution (2X15 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on an alumina column (14 g, hexanes-EtOAc 200:1) to give compound **29** (0.1 g, 95%) as a colorless oil: $[\alpha]_D^{25}$ +0.25 (*c* 0.47, $CHCl_3$) {lit[10b] $[\alpha]_D^{23}$ +0.24 (*c* 5.18, $CHCl_3$)}; ^1H NMR ($CHCl_3$) δ 0.83 (s, 3H), 0.86 (s, 3H), 0.92 (s, 3H), 0.98 (d, *J* = 6.6 Hz, 1H), 1.10-2.00 (m, 11H), 2.09 (q, *J* = 6.6 Hz, 1H), 2.46-2.49 (m, 2H), 3.15 (br s, 1H), 3.89-3.99 (m, 4H), 6.26 (s, 1H), 7.19 (s, 1H), 7.31 (s, 1H); ^{13}C NMR ($CHCl_3$) δ 7.18, 15.73, 18.40, 21.32, 21.71, 31.25, 31.56, 32.81, 33.19, 34.46, 41.42, 43.21, 43.47, 64.07, 65.30, 77.85, 110.89, 111.35, 125.91, 138.22, 142.41; MS *m/z* 362 (M^+). The spectroscopic data of synthetic **29** are in full agreement with those of the known compound.[10b]

(-)-(1*R*, 2*S*, 4a*S*, 8a*S*)-3-[3-(1,3-dioxolan-2-yl)-1,2,3,4,4a,5,6,7,8,8a-decahydro-1-hydroxy-2,5,5,8a-tetramethylnaphthyl-1-ethyl]-2-buten-4-olide (**31**).[10] To a stirred solution of compound **29** (360 mg, 1 mmol) in THF (22 mL) was added 1.6M *n*-BuLi in hexane (2.3 mL, 3.5 mmol) at -78°C. The mixture was stirred for 45 minutes. Me_3SiCl (0.04 mL, 0.7 mmol) was then added at -78°C. After 5 minutes, the reaction was quenched with brine (9 mL), extracted with Et_2O (3X20 mL), dried over $MgSO_4$, and evaporated. The residue, was chromatographed on silica gel (36 g, hexanes-EtOAc 50:1) to afford compound **30** (200 mg, 88% based on 54% conversion) as a colorless oil: $[\alpha]_D^{25}$ -16.5 (*c* 0.33, $CHCl_3$); ^1H NMR ($CHCl_3$) δ 0.23 (s, 9H), 0.84 (s, 3H), 0.87 (s, 3H), 0.94 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 1H), 1.25-2 (m, 11H), 2.11 (q, *J* = 6.9 Hz, 11H), 2.47-2.49 (m, 2H), 3.25 (br s, 1H), 3.91-4.03 (m, 4H), 6.50 (s, 1H), 7.39 (s, 1H); ^{13}C NMR ($CHCl_3$) δ -1.63, 7.28, 15.88, 18.49, 21.42, 21.82, 31.38, 31.68, 32.92, 33.29, 34.71, 41.52, 43.33, 43.55, 64.19, 65.41, 78.01, 110.98, 111.50, 121.06, 125.90, 142.57; MS *m/z* 434 (M^+). Compound **30** was oxidized immediately without further purification. To a stirred solution of 32% $MeCO_3H$ in HOAc (0.1 mL, 2 mmol) and powdered anhydrous NaOAc (160 mg, 2 mmol) in CH_2Cl_2 (20 mL) at 0°C was added a solution of **30** (200 mg, 0.5 mmol) in CH_2Cl_2 (3 mL). After stirring for 5 hours, sat. aq. $NaHCO_3$ solution (10 mL), and 10% $Na_2S_2O_3$ (10 mL) were added. The aq. layer was extracted with Et_2O (3X20 mL). The combined extract was washed with brine (2X20 mL), dried over $MgSO_4$ and evaporated. Chromatography of the residue on a silica gel column (5 g, hexanes-EtOAc 10:1) provided compound **31** (110 mg, 78% based on 78% conversion) as a colorless oil: $[\alpha]_D^{25}$ -0.21 (*c* 0.42, $CHCl_3$) {lit[10b] $[\alpha]_D^{25}$ -0.23 (*c* 17.0, $CHCl_3$)};^1H NMR ($CHCl_3$) δ 0.83 (s, 3H), 0.87 (s, 3H), 0.92 (s, 4.5H), 0.94 (s, 1.5H), 1.25-2 (m, 11H, 2.07 (q, *J* = 6.6 Hz, 1H), 2.35-2.5 (m, 2H), 3.36 (br s, 1H), 3.92-4.02 (m, 4H), 4.74 (s, 1H), 5.80 (t, *J* = 1.4 Hz, 1H); ^{13}C NMR ($CHCl_3$) δ 7.32, 15.70, 18.42, 21.73, 25.22, 31.23, 31.37, 31.58, 32.94, 33.21, 41.44, 43.32, 43.42, 43.92, 64.22, 65.43, 73.37, 77.58, 111.17,

114.64, 172.18, 174.42; MS *m/z* 378 (M^+). The spectroscopic data of synthetic **31** are in full agreement with those of the known compound.[10b]

(+)-(1"*R*, 2"*S*, 4"a*S*, 8"a*S*, 2'*S*-(4,5,3',4',3",4",4a",5",6",7",8",8"a)-Dodecahydro-3"-(1,3-dioxolan-2-yl)-5-oxo-2",5",5",8"a-tetramethyldispiro[furan-3(2*H*),2'(5'*H*)-furan-5',1"(2"*H*)]-naphthalene (32) and (-)-(1"*R*, 2"*S*, 4"a*S*, 8"a*S*, 2'*R*)-(4,5,3',4',3",4",4a",5",6",7",8",8"a)-Dodecahydro-3"-(1,3-dioxolan-2-yl)-5-oxo-2",5",5",8"a-tetramethyldispiro[furan-3(2*H*),2'(5'*H*)-furan-5',1"(2"*H*)]-naphthalene (33).[10] A mixture of compound **31** (20 mg, 0.06 mmol), and DBU (20 mg, 0.12 mmol) in Et_3N (5 mL) was refluxed for 7 hours. Concentration of the reaction mixture and chromatography of the residue on a silica gel column (4 g, hexanes-EtOAc 8:1) afforded the known **32** (10 mg, 43%) and **33** (10 mg, 44%). The higher R_f isomer **32** was a colorless oil: ^1H NMR ($CHCl_3$) δ 0.66 (s, 3H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.85 (s, 3H), 0.92 (s, 3H), 1.18-1.55 (m, 6H), 1.69-1.84 (m, 3H), 1.95-2.12 (m, 4H), 2.16-3.01 (ABq, *J* = 17.1 Hz, 2H), 3.70-3.81 (m, 1H), 3.89-4.01 (m, 4H), 4.12-4.45 (ABq, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CHCl_3$) δ 8.0, 17.2, 18.5, 21.9, 30.7, 31.7, 32.7, 32.8, 33.0, 38.7, 41.6, 42.2, 42.9, 43.4, 43.5, 63.9, 65.4, 78.9, 86.4, 95.0, 110.7, 174.5; MS *m/z* 378 (M^+). The lower R_f isomer **33** was also a colorless oil: ^1H NMR ($CHCl_3$) δ 0.80 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 3H), 0.94 (s, 3H), 1.15-1.20 (m, 2H), 1.34-1.58 (m, 5H), 1.60-1.70 (m, 3H), 2.02-2.54 (m, 4H), 2.47-3.16 (ABq, *J* = 17.3 Hz, 2H), 3.75-3.85 (m, 1H), 3.92-4.01 (m, 3H), 4.03-4.35 (ABq, *J*=8.5 Hz, 2H); ^{13}C NMR ($CHCl_3$) δ 8.3, 17.1, 18..5, 22.0, 30.8, 31.8, 32.4, 32.8, 33.1, 38.7, 41.7, 42.2, 42.2, 43.8, 64.0, 65.5, 76.5, 78.4, 88.6, 95.0, 110.7, 174.6, MS *m/z* 378 (M^+). The spectroscopic data of synthetic **32** and **33** are in full agreement with those of the known compounds.[10b]

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24. The following chiral bases have been used in the intramolecular Michael cyclization. These bases were kindly supplied by Professor Dr. Jürgen Martens, Fachbereich Chemie, Universität Oldenburg, Germany.