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A Phosphine-Catalyzed [3+2] Cycloaddition Strategy Leading to the First Total Synthesis of (−)-Hinesol

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Abstract: In one step, the skeleton of *cis*-spirovetivanes was constructed with high stereoselectivity by the phosphine-catalyzed [3+2] cycloaddition reaction of *tert*-butyl 2,3-butadienoate or 2-butynoate with 3-methyl-2-methylenecyclohexanone (**5**). This method was exemplified by the first highly efficient total synthesis of natural product (−)-hinesol, which is an active ingredient of cerebral circulation and metabolism improvers.

Spiro carbocycles are structures of broad synthetic and pharmaceutical interests.[1] Spirovetivanes, as one group of spiro[4.5]decane sesquiterpenes, are structurally recognized by a methyl group at C_{10} and an isopropyl group at C_2. The *cis*-spirovetivanes, which have the cis relative stereochemistry of the methyl group and the C_1-C_5 bond, include (−)-hinesol (**1**),[2,3] hinesene,[4] *β*-vetivone,[2,3] *β*-vetispirene,[5] etc. (−)-Hinesol, an important component of the Chinese crude drug Chang Zhu (Atractylodes lancea var Chinensis) and Baizhu (A. Japonica) was isolated almost a half century ago.[6] Recently, it was found out that (−)-hinesol, a spasmolytic[7] and anti-gastric ulcer[8] substance, is a relatively specific inhibitor of H^+, K^+-ATPase[8] and an active ingredient of cerebral circulation and metabolism improvers.[9] Many syntheses of the racemic hinesol[2,3] have been reported,[10] but few of them gave satisfactory results due to the low efficiency in constructing the spiro carbocyclic skeleton. Most of the target molecules are obtained as stereoisomeric mixtures. Herein, we wish to report an efficient and practical method of constructing spiro carbocyclic skeletons of *cis*-spirovetivanes and its application in the first total asymmetric synthesis of (−)-hinesol (**1**).[11]

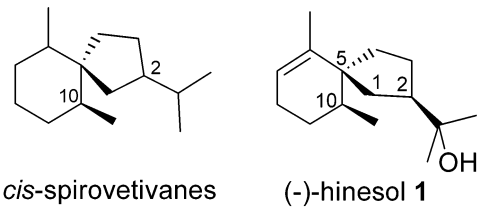

FIGURE 1. *cis*-Spirovetivanes and (−)-hinesol (**1**).

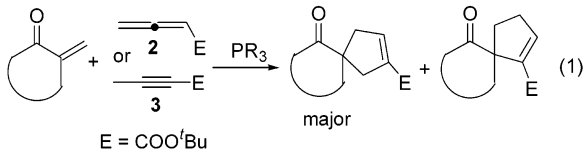

FIGURE 2. The synthesis of spirocycles.

A phosphine-catalyzed [3+2] cycloaddition reaction of 2,3-butadienoate or 2-butynoate with electron-deficient alkenes was discovered by our group.[12] Recently, an efficient entry to spiro carbocycles was achieved by the application of this method.[13] It revealed that while a bulky group such as *tert*-butyl was introduced into the three-carbon synthon, the regioselectivity of the cycloaddition reaction was greatly improved (Figure 2).

According to the retrosynthetic analysis, our synthetic strategy relies on the keto ester **4** as the key precursor of the spiro carbocyclic skeleton of *cis*-spirovetivanes, which might be conveniently constructed by the phosphine-catalyzed [3+2] cycloaddition of **5** (Scheme 1).

Thus, the reactions of the racemic **5** with compound **2** or **3** in the presence of phosphines under different conditions were studied. Four products **6**−**9** were obtained as assigned from ^{1}H NMR spectra (Scheme 2).[14] The cycloaddition of **5** and **3** catalyzed by tributylphosphine gave the higher yield (63%) of products in high

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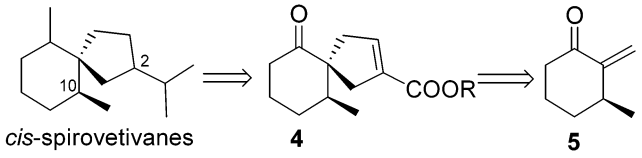
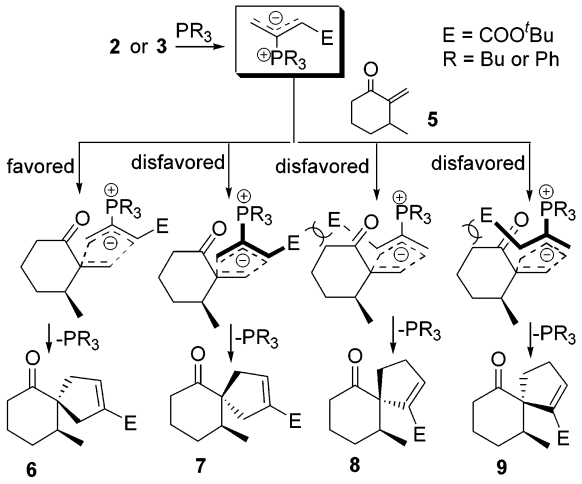
SCHEME 1. Retrosynthetic Analysis



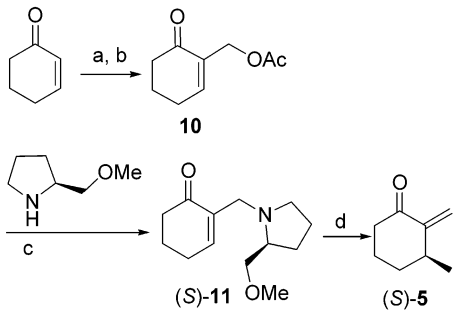
SCHEME 2. [3+2] Cycloaddition of 5



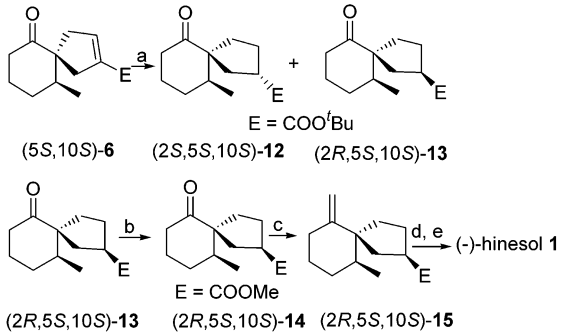
regio- and stereoselectivity (**6**/**7** 94/6). The structure of **6** was confirmed by X-ray crystallography. It might be rationalized that the 1,3-dipole approaches to the face of olefin from the opposite side of the methyl group and the bulky ester group of the 1,3-dipole should be far away from the cyclohexanone skeleton due to the steric hindrance (Scheme 2).[15] Thus, the spiro carbocycle with specific stereochemistry in the six-membered ring was constructed efficiently in one step, indicating that this is a highly efficient method for preparing substituted spiro[4.5]decane derivatives, especially the skeleton of *cis*-spirovetivanes. With compound **6** in hand, the synthesis of (±)-hinesol was successfully realized by further transformations (see Supporting Information).

For the synthesis of optically active (−)-hinesol (**1**), homochiral (*S*)-**5** was chosen as the starting material. Starting from 2-cyclohexenone, compound **10** was easily obtained via a Morita−Baylis−Hillman reaction followed by the protection of the resulting alcohol.[16] Then, in the presence of 2.1 equiv of (*S*)-2-(methoxymethyl)pyrrolidine, compound **10** was converted to compound (*S*)-**11** via an S_N2 process, which was further converted to (*S*)-**5** (95% ee), the corresponding chiral starting material for constructing the chiral spiro carbocycle (Scheme 3).[17] Tributylphosphine-catalyzed [3+2] cycloaddition of (*S*)-**5** with

SCHEME 3. Synthesis of (*S*)-3-Methyl-2-methylenecyclohexanone ((*S*)-5)



SCHEME 4. The Synthesis of (−)-Hinesol 1[a]



[a] Reagents and conditions: (a) Pd/C (5%, w/w), 1 atm of H_2, MeOH, rt (99%, **12**/**13**: 13/87). (b) Cat. H_2SO_4, MeOH, reflux (93%). (c) $Zn/CH_2I_2/TiCl_4$, CH_2Cl_2/THF (82%). (d) *p*-TsOH, benzene, reflux. (e) MeMgI, Et_2O, 0 °C to room temperature (87% from **14**).

tert-butyl 2-butynoate gave (5*S*,10*S*)-**6** in about 60% yield with 94% ee.[18] Hydrogenation of the spiro carbocycle (5*S*,10*S*)-**6** over palladium on charcoal (5%, w/w) in methanol afforded a mixture of diastereomers (2*S*,5*S*,10*S*)-**12** and (2*R*,5*S*,10*S*)-**13** (**12**/**13** 13:87). The stereoselectivity observed during the hydrogenation of **6** to **12** and **13** might be rationalized by the solvation of the polarized carbonyl group of **6**, which creates a steric barrier to catalyst binding from that face of the cyclopentene double bond.[19] The major *tert*-butyl ester **13** was converted to methyl ester (2*R*,5*S*,10*S*)-**14** by ester exchange. Compound (2*R*,5*S*,10*S*)-**14** was then treated with $Zn/CH_2I_2/TiCl_4$[20] to afford product (2*R*,5*S*,10*S*)-**15**.[10o] The exo-olefin (2*R*,5*S*,10*S*)-**15** was readily isomerized to endo-olefin with *p*-TsOH in refluxing benzene, which was subsequently subjected to methylmagnesium iodide to achieve the total synthesis of (−)-hinesol (**1**) (94% ee, $[\alpha]_D$ −40 (*c* 0.25, $CHCl_3$); lit. $[\alpha]_D$ −40.2 (*c* 10.0, $CHCl_3$),[6a] $[\alpha]_D$ −47.8 (*c* 5.104, $CHCl_3$)[6b]) in 10 steps and 22% overall yield from 2-cyclohexenone (Scheme 4).[21]

In conclusion, a highly efficient approach to construct the skeleton of *cis*-spirovetivanes via a phosphine-

(14) The results of reactions of **5** with **2** or **3** under different conditions were outlined as follows. Condition A (a solution of **5** (1.0 mmol), **2** (1.2 mmol), and PPh_3 (0.10 mmol, 10 mol %) in dry toluene (10 mL) was stirred under reflux): total yield 23%; ratio of **6**/**7**/**8**/**9** (determined by ^1H NMR spectra) 73/12/12/3. Condition B (a solution of **5** (1.0 mmol), **2** (1.2 mmol), and PBu_3 (0.10 mmol, 10 mol %) in dry toluene (10 mL) was stirred at room temperature): total yield 41%; ratio of **6**/**7**/**8**/**9** 83/10/7/0. Condition C (a solution of **5** (1.0 mmol), **3** (1.2 mmol), and PBu_3 (0.10 mmol, 10 mol %) in dry toluene (10 mL) was stirred at room temperature): total yield 63%; ratio of **6**/**7**/**8**/**9** 94/6/0/0.

(15) For a detailed mechanism of phosphine-catalyzed [3+2] cycloaddition, see ref 12b.

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(18) The ee value of (5*S*,6*S*)-**6** was determined by HPLC analysis (column, CHIRALPAK AD) with 100:1 hexane:2-propanol as eluent.

(19) Similar results were observed, see refs 10d and 10o.

(20) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579.

(21) The ee value of (−)-hinesol was determined by GC analysis (column CHIRALCEL DEX B−PH (astec)) with N_2 (8.0 psi) as carrier gas.

catalyzed [3+2] cycloaddition reaction was developed. The utility of this method was exemplified by the first total synthesis of natural product (−)-hinesol (**1**), which features a rapid and efficient construction of the spiro carbocyclic skeleton.

Experimental Section

The detailed procedures in the synthesis of (±)-hinesol are described in the Supporting Information.

(*S*)-2-((2′-(Methoxymethyl)-1′-pyrrolidinyl)methyl)cyclohex-2-en-1-one ((*S*)-11).[17] To compound **10** in acetonitrile (10 mL) was added (*S*)-2-(methoxymethyl)pyrrolidine (10.5 mmol) at 25 °C. The reaction mixture was stirred for 1 h and concentrated in vacuo. The oily residue was diluted with ethyl acetate (30 mL) and washed with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give compound **11** in nearly quantitative yield.

(*S*)-3-Methyl-2-methylenecyclohexenone ((*S*)-5).[17] (*S*)-3-Methyl-2-methylenecyclohexenone ((*S*)-**5**) was prepared by the reported method.[17] Oil; yield 67%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (br s, 1H), 5.13 (br s, 1H), 2.60−2.46 (m, 2H), 2.35 (m, 1H), 2.03−1.73 (m, 4H), 1.15 (d, J = 6.7 Hz, 3H). 94.6% ee (lit.[17] 95% ee). The ee value of (*S*)-**5** was determined by first converting (*S*)-**5** to *cis*-2-benzyl-3-methylcyclohexanone and by HPLC analysis of the cyclohexanone derivative (crude product) with the same method as that of the literature.[17] HPLC: column, CHIRALCEL OJ (4.6 mm i.d. × 250 mm, Daicel Chemical Industries); eluent, 95:5 hexane:2-propanol; flow rate, 0.7 mL/min; detecting, 214-nm light.

***tert*-Butyl (5*S*,10*S*)-10-Methyl-6-oxo-spiro[4.5]dec-2-ene-2-carboxylate ((5*S*,10*S*)-6).** A solution of (*S*)-**5** (1.2 mmol), **3** (1.0 mmol), and PBu_3 (0.1 mmol) in dry toluene (10 mL) was stirred at room temperature for 23 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give 166 mg of a mixture of compounds **6** and **7** in a 63% total yield (**6**/**7** 94/6). Compound (5*S*,10*S*)-**6** was isolated by further column chromatography on silica gel with petroleum ether and ethyl acetate as the eluent. Oil. IR (neat) ν 2975, 2934, 1706, 1639, 1172 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57−6.54 (m, 1H), 3.47 (d, J = 19.3 Hz, 1H), 2.76 (d, J = 17.1 Hz, 1H), 2.52−2.38 (m, 3H), 2.19 (d, J = 19.3 Hz, 1H), 2.00−1.97 (m, 1H), 1.75−1.60 (m, 4H), 1.47 (s, 9H), 0.91 (d, J = 6.1 Hz, 3H). MS (*m*/*z*) 208 ($M^+ - C_4H_8$), 191 ($M^+ - O^tBu$), 190, 124, 91, 77, 65, 57 (100), 41. $[\alpha]_D$ −29.7 (*c* 0.750, $CHCl_3$). 93.6% ee. HPLC (crude product): column, CHIRALPAK AD (4.6 mm i.d. x 250 mm, Daicel Chemical Industries); eluent, 100:1 hexane:2-propanol; flow rate, 0.5 mL/min; detecting, 214-nm light.

***tert*-Butyl (2*S*,5*S*,10*S*)-10-Methyl-6-oxo-spiro[4.5]decane-2-carboxylate ((2*S*,5*S*,10*S*)-12) and *tert*-Butyl (2*R*,5*S*,10*S*)-10-Methyl-6-oxo-spiro[4.5]decane-2-carboxylate ((2*R*,5*S*,6*S*)-13).** The spiro olefin **6** (214 mg, 0.81 mmol) was hydrogenated over Pd/C (5%, 40 mg) in 5 mL of MeOH at room temperature. The resulting mixture was filtered on silica gel and washed with ethyl acetate three times, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether (60−90 °C) 1/50) affording a minor product (**12**) (25 mg, 12%) and a major product (**13**) (188 mg, 87%). (2*S*,5*S*,10*S*)-**12**: Oil. IR (neat) ν 2972, 1726, 1704, 1154 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71−2.66 (m, 1H), 2.54−2.46 (m, 1H), 2.38−2.31 (m, 2H), 2.15−2.10 (m, 1H), 2.00−1.80 (m, 3H), 1.78−1.73 (m, 4H), 1.57−1.37 (m, 11H), 0.92 (d, J = 7.0 Hz, 3H). MS (*m*/*z*) 210 ($M^+ - C_4H_8$), 193 ($M^+ - O^tBu$), 192, 165, 164, 147, 57 (100), 41. $[\alpha]^{20}_D$ +25.3 (*c* 0.55, $CHCl_3$). (2*R*,5*S*,10*S*)-**3**: Oil. IR (neat) ν 2968, 2937, 1728, 1706, 1155 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69−2.58 (m, 1H), 2.48−2.39 (m, 2H), 2.36−2.29 (m, 1H), 2.07−1.65 (m, 8H), 1.58−1.44 (m, 2H), 1.43 (s, 9H), 0.94 (d, J = 6.9 Hz, 3H). MS (*m*/*z*) 210 ($M^+ - C_4H_8$), 193 (2), 147, 125, 57 (100), 55, 41. $[\alpha]^{20}_D$ +11.3 (*c* 0.42, $CHCl_3$).

Methyl (2*R*,5*S*,10*S*)-10-Methyl-6-oxo-spiro[4.5]decane-2-carboxylate ((2*R*,5*S*,10*S*)-14). *tert*-Butyl ester **13** (309 mg, 1.16 mmol) was directly converted to the methyl ester by ester exchange in refluxing methanol (2.5 mL) in the presence of a catalytic amount of concentrated H_2SO_4. After 24 h, the resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel affording (2*R*,5*S*,10*S*)-**14** as a colorless oil. Yield 93%. Oil. IR (neat) ν 2955, 1735, 1705, 1214, 1170 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.74 (m, 1H), 2.42 (t, J = 6.8 Hz, 2H), 2.34 (ddd, J = 12.9, 7.6, 3.0 Hz, 1H), 2.12 (dd, J = 13.5, 7.9 Hz, 1H), 2.00−1.65 (m, 7H), 1.60−1.47 (m, 2H), 0.96 (d, J = 7.1 Hz, 3H). MS (*m*/*z*) 224 (M^+), 147, 125 (100), 108, 93, 79, 67, 55, 41. $[\alpha]^{20}_D$ +10 (*c* 0.156, $CHCl_3$).

Methyl (2*R*,5*S*,10*S*)-10-Methyl-6-methylenespiro[4.5]decane-2-carboxylate ((2*R*,5*S*,10*S*)-15). CH_2I_2 (0.32 mL) was added at 25 °C to a stirring suspension of zinc (freshly activated, 0.48 g, 7.2 mmol) in THF (8 mL) under an argon atmosphere. After 0.5 h, a solution of $TiCl_4$ (1 M solution in CH_2Cl_2, 0.74 mL) was added at 0 °C and the resulting brown mixture was stirred at room temperature for 30 min. Ester (2*R*,5*S*,10*S*)-**14** (80 mg, 0.36 mmol) in THF (2 mL) was added dropwise to the above mixture at room temperature. After 15 min, the reaction mixture was diluted with Et_2O and the reaction was quenched by saturated NH_4Cl solution. Then, the resulting mixture was separated and the organic layer was concentrated under reduced pressure. The product was purified by column chromatography on silica gel affording (2*R*,5*S*,10*S*)-**15** as a colorless oil in an 82% yield. Oil. IR (neat) ν 2935, 1737, 1639, 1201, 1170 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (s, 1H), 4.63 (s, 1H), 3.67 (s, 3H), 2.80 (m, 1H), 2.22−2.14 (m, 2H), 2.10−1.30 (m, 11H), 0.86 (d, J = 7.3 Hz, 3H). MS (*m*/*z*) 222 (M^+), 162, 107, 95 (100), 91, 82, 81, 79, 67. $[\alpha]^{20}_D$ +30.9 (*c* 0.547, $CHCl_3$).

(−)-Hinesol ((−)-1). Compound **15** (28 mg, 0.13 mmol) was added to a mixture of TsOH (4 mg) in benzene (4 mL) at room temperature. After 10 h of refluxing, the resulting mixture was chromatographed on silica gel, affording endo-olefin (26 mg) as a colorless oil in a 93% yield. The endo-olefin (18 mg) in Et_2O (2 mL) was added dropwise to an ice-cold solution of methylmagnesium iodide (16 equiv) in dry ether (16 mL). The mixture was stirred for 30 min at 0 °C and then at room temperature for 3 h. A few drops of water were added to the reaction mixture to quench the reaction. After the mixture was stirred for 15 min, the resulting mixture was dried ($MgSO_4$) and concentrated under vacuum. The residue was chromatographed on silica gel (eluent: *n*-hexane/ethyl acetate 10/1) to afford **1** (17 mg) as a colorless oil in a 94% yield. Oil. IR (ref 10f), ^{1}H NMR (refs 10n and 10o), and ^{13}C NMR (ref 10k) data were identical with those of the literature. IR (neat) ν 3399, 2964, 2926, 2877, 1660, 1468, 1457, 1378, 1134, 937, 917, 799. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (br s, 1H), 2.10−1.91 (m, 3H), 1.79−1.26 (m, 13H), 1.21 (s, 6H), 0.92 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 121.6, 72.0, 51.4, 48.7, 36.7, 35.6, 33.2, 28.4, 28.0, 27.9, 27.6, 24.2, 19.9, 16.2. MS (*m*/*z*) 222 (M^+), 161 (100), 147, 119, 107, 93, 91, 59, 43. $[\alpha]^{20}_D$ −40 (*c* 0.25, $CHCl_3$) (lit.[6a] $[\alpha]_D$ −40.2 (*c* 10.0, $CHCl_3$); lit.[6b] $[\alpha]_D$ −47.8 (*c* 5.104, $CHCl_3$)). The ee value of (2*R*,5*S*,10*S*)-**1** was determined by GC analysis. GC:column, CHIRALCEL DEX B-PH (astec), 0.25 mm i.d. × 20 m, PE Autosystem X L; carrier gas, N_2 (8.0 psi); column temperature, 250 °C; detector temperature, 250 °C.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds; copies of ^{1}H NMR spectra, ^{13}C NMR spectra, and chiral HPLC of (−)-hinesol synthesized; X-ray crystallography of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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