An Asymmetric Total Synthesis of Fragrant Spiro[4.5]decane Sesquiterpene (–)-β-Vetivone via an Enantiomerically Pure Vinylic Sulfoxide

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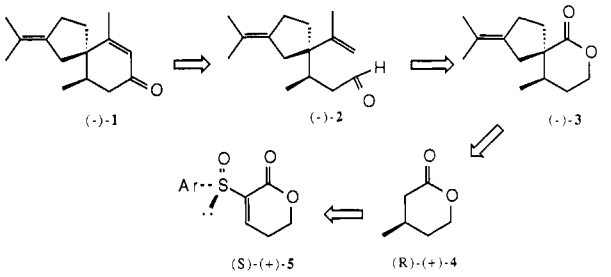
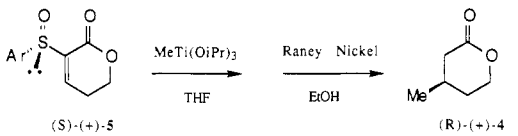
A nonenzymatic asymmetric synthesis of (*R*)-(+)-3-methylpentanolide **4** in 93% enantiomeric purity has been achieved involving novel methyltitanium triisopropoxide conjugate methyl addition to enantiomerically pure *p*-anisylpentenolide sulfoxide (*S*)-(+)-**5b**. One-step, five-membered ring spiroannulation then formed a quaternary carbon center in a stereospecific fashion to give spiroheterocycle (–)-**3**. Spiroheterocycle (–)-**3** was converted directly into natural spirocarbocycle (–)-β-vetivone, **1**, constituting the third asymmetric total synthesis of this commercially valuable fragrant sesquiterpene.

(–)-β-Vetivone produces the pleasant odor characteristic of the essence of vetiver oil,[1] which is of great value to the perfume,[2] soap,[2] and cosmetic[3] industries. Isolation of (–)-β-vetivone from plant sources is tedious, time-consuming and low-yielding, which accounts for the high cost of this fragrant oil.[2] Originally thought to be a hydroazulenic sesquiterpene, (–)-β-vetivone is actually a member of the well-populated and often biologically active spiro[4.5]decane family of natural products.[4] This family is apparently derived biogenetically via ring contraction of some decalin precursors.[4e] The flexibility, and therefore the usefulness, of the spiro[4.5]decane ring system as a synthetic intermediate has been established by its key role in total synthesis of the antitumor agent quadrone,[5] the neurotoxin perhydrohistrionicotoxin,[6] and some highly strained propellanes.[7] Because of its high commercial value and its structurally challenging and versatile spiro[4.5]decane ring system, β-vetivone has been the object of many synthetic efforts;[8] only two asymmetric total syntheses of (–)-β-vetivone, however, have been reported.[9]

Scheme I



Scheme II



	% yield	R : S	% ee
(S)-(+)-5a, Ar = p-Tolyl	44	3.4 : 1	55
(S)-(+)-5b, Ar = p-Anisyl	51	27 : 1	93

Our interest in using enantiomerically pure vinylic sulfoxides for asymmetric synthesis of sulfur-free natural products [e.g. (+)-α-cuparenone,[10] (–)-podorhizon,[11] (+)-methyl jasmonate,[12] (+)-estrone,[13] and (+)-A-factor[14]][15] led us to design an asymmetric total synthesis of (–)-β-vetivone in which chirality would be relayed from a stereogenic sulfoxide sulfur atom to a single stereogenic carbon atom and then to an adjacent quaternary carbon center, as suggested by retrosynthetic Scheme I. Specifically, stereocontrolled conjugate addition of a nucleophilic methyl group to enantiomerically pure lactone sulfoxide (*S*)-(+)-**5** was expected[11,16] to produce (*R*)-(+)-3-methylpentanolide **4** in high enantiomeric purity. This mono-

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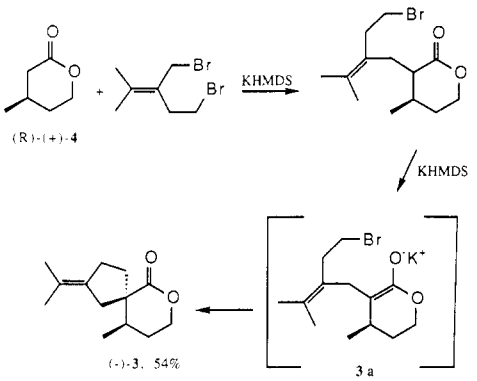
Scheme III

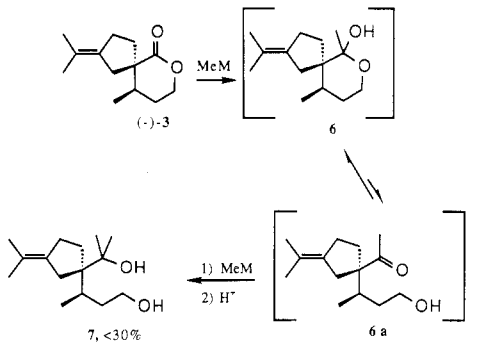


substituted, six-membered, lactone ring system was then anticipated to provide two crucial control elements: regiochemical control (i.e. enolization possible only toward the substituent methyl group, in contrast for example to enolization of 3-methylcyclohexanone) and stereochemical control. The stereocontrolled spiroannulation step was modeled on the Stork–Danheiser–Ganem efficient synthesis of racemic β-vetivone[8b] and involved a bifunctional allylic–homoallylic dihalide reacting first at the allylic electrophilic center and then, following precedent for C-alkylation trans to a β-substituent in the enolate of a six-membered ring carbonyl compound,[8b,17] at the homoallylic center to afford spiro adduct (–)-**3**. With the two desired asymmetric centers in place, introduction of the remaining 14th and 15th carbon atoms of the sesquiterpene skeleton was to lead in a straightforward and precedented fashion[8j] via cyclization of δ,ϵ-unsaturated aldehyde (–)-**2** into (–)-β-vetivone (**1**). We report here successful execution of this plan.

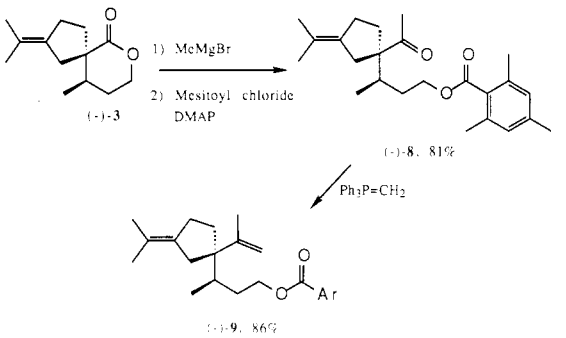
Results and Discussion

(*R*)-(+)-3-Methylpentanolide **4** was prepared by conjugate methyl addition to enantiomerically pure pentenolide sulfoxide **5** followed by reductive cleavage of the sulfinyl group (Scheme II).[18] Choice of methylmetallic reagents for this conjugate methyl addition centered on dimethylcopperlithium and, ultimately, on methyltitanium triisopropoxide; the powerful Michael acceptor character of metal-chelated pentenolide sulfoxides **5** directed even the organotitanium reagent toward conjugate rather than carbonyl addition.[19] As we have discussed previously,[15] the chelated and therefore rotationally locked conformer of β-keto sulfoxides (*S*)-(+)-(**5**) directs approach of the organometallic nucleophile to the *pro-R* face of the enoate β-carbon atom. Modest asymmetric induction was obtained with *p*-toluenesulfinyl lactone **5a**. Replacing the *p*-tolyl group by a more resonance electron-donating *p*-anisyl group (i.e. **5b**), leading presumably to a stronger metal chelate,[19] produced a truly dramatic increase in the level of asymmetric induction; the *R*:*S* ratio of product enantiomers **4** changed from 3:1 to 27:1 (Scheme II)! A previous attempt to use an enantiomerically pure vinylic sulfoxide to prepare (*R*)-3-methylpentanolide **4** led to only

Scheme IV



Scheme V



a 3:2 ratio of *R*:*S* enantiomers.[20] The enantiomeric purity of (*R*)-3-methylpentanolide was assayed polarimetrically as well as by preparing a derivative pair of diastereomers using an enantiomerically pure derivatizing agent.[21] The methyltitanium reagent used in Scheme II was found to be more effective than dimethylcopperlithium in promoting stereocontrolled introduction of the methyl group.[19] (*R*)-(+)-3-Methylpentanolide **4** can be prepared also by using esterase[22] or dehydrogenase[23] enzymes.

With (*R*)-(+)-3-methylpentaniolide **4** in hand, we turned to the spiroannulation step. An allylic–homoallylic biselectrophile was used (Scheme III). Enolization of lactone **4**, C-allylation, and subsequent in situ enolization produced enolate ion intermediate **3a**. Intramolecular C-alkylation (i.e. cyclization) of this enolate ion occurred stereospecifically trans to the adjacent methyl group as anticipated based on stereoelectronic considerations and on literature precedent,[8b,17] thereby relaying absolute stereochemistry from the tertiary stereogenic center to the newly formed adjacent quaternary carbon center.

Various approaches can be envisioned for introduction of the remaining 14th and 15th carbon atoms of the sesquiterpene skeleton of β-vetivone. Conversion of the lactone ring of spiroheterocycle (–)-**3** into the required 3-methylcyclohexenone ring of spirocarbocyclic β-vetivone was planned via cyclization of 15-carbon atom δ,ϵ-olefinic aldehyde (–)-**2**; such cyclization had been done before on racemic **2**. Transformation of spirolactone (–)-**3** into olefinic aldehyde (–)-**2**, however, posed some unexpected problems. Attempts to convert spirolactone (–)-**3** into primary–tertiary diol **7** with either methyllithium or methylmagnesium bromide produced major amounts of lactol **6** (Scheme IV). Apparently the five-membered ring holds its *geminal* substituents sufficiently close so that the usual

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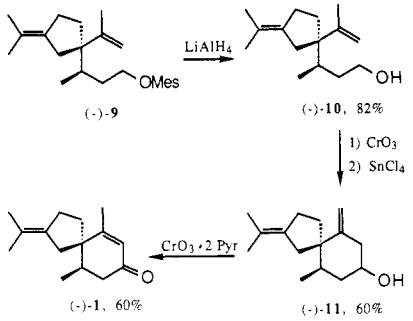
Scheme VI



lactol–hydroxyketone equilibrium (i.e. **6** ⇌ **6a**) lies predominantly on the lactol side. Molecular models and literature analogy[24] support this explanation for the ineffectiveness of Scheme IV in producing useful amounts of diol **7**. Likewise, attempts to trap hydroxy ketone **6a** with methylenetriphenylphosphorane failed.

Hydroxy ketone **6a** was effectively trapped, however, with mesitoyl chloride to form sterically hindered keto ester (−)-**8** (Scheme V). The sterically encumbered ketone carbonyl group in keto ester (−)-**8** did not undergo typical carbonyl addition with methyllithium, methylmagnesium bromide, [(trimethylsilyl)methyl]magnesium chloride,[25] methyltitanium triisopropoxide,[26] tetramethyltitanium,[26] tetramethylzirconium,[27] zinc dibromomethane/titanium tetrachloride,[28] 2-lithio-1,3-dithiane,[29] or [(phenylthio)-methyl]lithium.[30] In some of these attempts, quenching the reaction mixture with deuterium oxide showed that ketone enolization was occurring. Finally, conditions were found for successful salt-free Wittig methylenation[31] to produce olefinic ester (−)-**9** (Scheme V).

Reduction of mesitoate ester (−)-**9** produced primary alcohol (−)-**10** (Scheme VI). Chromium trioxide pyridine oxidation[32] followed immediately by tin tetrachloride promoted cyclization[33] gave spirobicyclic homoallylic alcohol (−)-**11** (Scheme VI). The total synthesis was consummated by chromium trioxide/pyridine oxidation[34] to form (−)-β-vetivone, identical in physical and spectroscopic properties with a sample of natural (−)-β-vetivone kindly provided by the Givaudan Corp.

Conclusion

The viability of a novel approach to the spiro[4.5]decane structural system has been demonstrated by an asymmetric total synthesis of (−)-β-vetivone. The synthetic plan involved critical use of new, enantiomerically pure, six-membered, unsaturated sulfinyl lactone (*S*)-(+)-**5b** for two essential reactions: as a template for highly stereocontrolled asymmetric conjugate methyl addition (**5** → **4**) and then as a rigid six-membered ring enolate ion for stereospecific spiroannulation (**4** → **3**). Having performed its function of controlling first the absolute and then the relative stereochemistry of two adjacent tertiary and quaternary carbon centers, the lactone ring was cleaved (**3** → **2**) and then was transformed into the six-membered carbocycle of (−)-β-vetivone (**1**). Some of the homochiral intermediates in this asymmetric synthesis of (−)-β-vetivone can be used for preparation of other spiro[4.5]decane natural products (e.g. β-vetispirene[35]).

Experimental Section[37]

(*S*)-(+)-Pentenolide Sulfoxide (5b). The synthesis of (*S*)-(+)-**5b** was carried out in the same manner as the synthesis of (*S*)-(+)-**5a**[18] with (S_S)-(−)-menthyl *p*-methoxybenzenesulfinate[19] in place of (S_S)-(−)-menthyl *p*-methylbenzenesulfinate.

Pentenolide sulfoxide (*S*)-(+)-**5b**: ^{1}H NMR (δ, $CDCl_3$) 7.72 (3 H, m), 7.01 (2 H, d, J = 8.82 Hz), 4.50 (1 H, m), 4.33 (1 H, m), 3.87 (3 H, s), 2.84 (1 H, m), 2.68 (1 H, m); ^{13}C NMR (δ, $CDCl_3$) 162.29, 159.98, 143.08, 139.24, 133.62, 127.47, 114.62, 66.16, 55.40, 24.68; IR ($CHCl_3$, cm^{-1}) 1715; $[\alpha]^{25}_D$ 242.9° (*c* 0.16, $CHCl_3$). Anal. Calcd for $C_{12}H_{12}O_4S$: C, 57.14; H, 4.76; S, 12.70. Found: C, 56.99; H, 4.85; S, 12.63. The enantiomeric purity (>98% ee) of (*S*)-(+)-**5b** was determined by using the chiral NMR shift reagent Eu(tfc)$_3$. Complexation of racemic pentenolide sulfoxide with 0.2 equiv of Eu(tfc)$_3$ produced two diastereotopic signals of equal intensity for the protons of the methoxy group at δ 3.97 and 3.93. Complexation of pentenolide sulfoxide (*S*)-(+)-**5b** with 0.2 equiv of Eu(tfc)$_3$ produced a similar downfield shift for the protons of the methoxy group (from δ 3.87 to 3.94) with only one diastereotopic resonance present.

(*R*)-(+)-3-Methyl-5-pentanolide (4). To a −78 °C solution of 6.24 mL (26.12 mmol) of chlorotitanium triisopropoxide in 39 mL of THF was added 18.5 mL (25.9 mmol) of 1.4 M methyllithium in diethyl ether via syringe pump over 35 min giving a clear orange-yellow solution, which eventually became opaque. After the mixture was stirred at −78 °C for 30 min, a −78 °C solution of 1.30 g (5.17 mmol) of (*S*)-(+)-**5b** in 39 mL of THF was added via cannula dropwise over 30 min. The cold bath was allowed to warm slowly to 0 °C over 4.5 h and then stirred at 0 °C for 1.5 h. The reaction was quenched slowly with 10% HCl, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated at 0 °C to give the conjugate adduct as a clear yellow liquid. Several milliliters of absolute ethanol were added, the mixture was cooled to 0 °C and was treated with about 10 mL of Raney nickel. The reaction was warmed to room temperature over approximately 45 min and stirred at room temperature for 1 h. The ethanol was decanted; the Raney nickel was rinsed with absolute ethanol and decanted. This was repeated several times. The ethanol was distilled off at atmospheric pressure to give 810 mg of (*R*)-(+)-**4** as a brown liquid. A ^{1}H NMR yield with tris(phenylthio)methane as the internal standard gave an 82% yield of (*R*)-(+)-**4**. Prepartive gas chromatography (15% SE 30 on Chromosorb W, 30/60, 20 ft × $^3/_8$ in., carrier gas (He) flow rate 50 mL/min, column temperature 200 °C, t_R 19.5 min) yielded 299.3 mg (51%) of (*R*)-(+)-**4** as a clear, colorless liquid: ^{1}H NMR (δ, $CDCl_3$) 4.5–4.2

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(37) Melting points and boiling points are uncorrected. ^{1}H NMR spectra were obtained at 80 or 400 MHz. ^{13}C NMR spectra were recorded at 100 MHz. The tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. The methylene chloride, pyridine, benzene, and hexamethylphosphoramide (HMPA) were distilled from calcium hydride prior to use. The absolute ethanol was purchased from The Warner-Graham Co., Cockeysville, MD, and was used as received. The Raney nickel was a gift of The W. R. Grace Co., and the mesitoyl chloride was purchased from Lancaster Synthesis. The following chemicals were purchased from Aldrich Chemical Co. and used as received: chlorotitanium triisopropoxide, tris(phenylthio)methane, potassium bis(trimethylsilyl)amide (0.5 M in toluene), phosphorus tribromide, 4-(dimethylamino)pyridine, potassium hydride (35 wt % dispersion in mineral oil), methyltriphenylphosphonium bromide, lithium aluminum hydride (1.0 M in diethyl ether), chromium trioxide, tin(IV) chloride (1.0 M in methylene chloride), methylmagnesium bromide (3.0 M in diethyl ether), and methyllithium (1.4 M in diethyl ether). The methyllithium was tritrated with anhydrous diphenylacetic acid[36] (Aldrich Chemical Co.) prior to use. Preparative TLC plates were purchased from Analtech, and the silica gel used for column chromatography was Merck Kieselgel 60 purchased from Bodman Chemical Co.

(2 H, m), 2.8–1.2 (5 H, m), 1.06 (3 H, d, J = 5.9 Hz); IR ($CHCl_3$, cm^{-1}) 1730; $[\alpha]^{26}_D$ 25.9° (c 0.61, $CHCl_3$). The enantiomeric purity of (R)-(+)-4 was determined by converting (R)-(+)-4 into the corresponding primary–tertiary diol (3 equiv of MeLi) and then into the corresponding primary Mosher ester. The ^{19}F NMR spectrum of this Mosher ester showed two singlets (δ 96.85 and 96.78) in a ratio of 27:1 (compared to a ratio of 1.00:1.02 for the Mosher ester of this diol derivative of racemic 4), indicating a diastereomeric excess of 93%.

(5R,10R)-(−)-10-Methyl-2-(1-methylethenyl)-7-oxaspiro[4.5]decan-6-one (3). To a solution of 142.2 mg (1.25 mmol) of (R)-(+)-4 in 3 mL of THF at −78 °C was added 2.95 mL (1.48 mmol) of 0.5 M potassium bis(trimethylsilyl)amide in toluene via a syringe pump over 10 min. The reaction mixture was stirred for 50 min and was then treated with a solution of 792.3 mg (3.09 mmol) of 2-methyl-3-(bromomethyl)-5-bromo-2-pentene (prepared from the corresponding diol[8b] with phosphorous tribromide in diethyl ether from 0 °C to room temperature) in 1.2 mL of THF containing 870 μL (5 mmol) of HMPA via a syringe pump over 15 min. The reaction was warmed slowly to room temperature overnight, giving a white opaque mixture. The reaction mixture was stirred for a total of about 24 h. The reaction mixture was cooled to −78 °C, and 2.94 mL (1.48 mmol) of 0.5 M potassium bis(trimethylsilyl)amide in toluene was added. The reaction was warmed slowly to room temperature and stirred overnight (about 24 h), giving a white opaque mixture. The reaction was quenched with aqueous saturated ammonium chloride, diluted with water, extracted with diethyl ether, washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 505.7 mg of a yellow liquid. Purification by column chromatography (4 g of silica, 5:1 hexane–diethyl ether) gave 140.1 mg (54%) of (−)-3 as a white solid having the same spectral properties as an analytically pure sample. A portion of this was recrystallized from pentane to yield (−)-3 as a white solid: mp 53–55 °C; ^1H NMR (δ, $CDCl_3$) 4.47–4.35 (2 H, m), 1.63 (6 H, s), 2.8–0.8 (9 H, m), 1.08 (3 H, d, J = 6.9 Hz); ^{13}C NMR (δ, $CDCl_3$) 176.4, 133.11, 121.86, 66.67, 54.05, 38.11, 37.70, 35.63, 28.99, 27.56, 20.93, 20.87, 16.23; IR ($CHCl_3$, cm^{-1}) 1720; $[\alpha]^{26}_D$ −75.76° (c 0.33, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.72; H, 9.47.

(5R,10R)-(−)-3-Methyl-3-[1-acetyl-3-(1-methylethylidene)cyclopentyl]propyl Mesitoate (8). A solution of 29.7 mg (0.14 mmol) of (−)-3 in 820 μL of THF at room temperature was treated with 63 μL (0.17 mmol) of 2.7 M methylmagnesium bromide in diethyl ether. After the mixture was stirred at room temperature for 1.5 h, a solution of 224.5 mg (1.23 mmol) of mesitoyl chloride in 300 μL of THF containing a catalytic amount of 4-(dimethylamino)pyridine was added. After being stirred overnight at room temperature, the brown opaque mixture was quenched with aqueous saturated ammonium chloride and extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 196 mg of an off white solid. Purification by column chromatography (4 g silica, 10:1 hexane–diethyl ether) yielded 42.7 mg (80.7%) of (−)-8 as a clear, yellow oil: ^1H NMR (δ, $CDCl_3$) 6.84 (2 H, s), 4.39 (1 H, m), 4.27 (1 H, m), 2.28 (6 H, s), 2.27 (3 H, s), 2.11 (3 H, s), 1.62 (3 H, s), 1.55 (3 H, s), 0.95 (3 H, d, J = 6.8 Hz), 2.8–1.0 (9 H, m); IR ($CHCl_3$, cm^{-1}) 1705, 1690 (sh); HRMS calcd for $C_{23}H_{34}O_3$ m/e 370.2508, found 370.2510; $[\alpha]^{26}_D$ −14.87° (c 0.77, $CHCl_3$).

(5R,10R)-(−)-3-Methyl-3-[1-(1-methylethenyl)-3-(1-methylethylidene)cyclopentyl]propyl Mesitoate (9). A slurry of 897 mg (22.4 mmol) of potassium hydride (washed with pentane five times) in 32 mL of THF at room temperature was treated with 8.98 g (25.1 mmol) of methyltriphenylphosphonium bromide via a solid addition funnel over 10 min. The slurry was stirred 2 h at room temperature and then at 50 °C for 30 min. The bright yellow slurry was cooled to room temperature, 9.5 mL of benzene was added, and this slurry was transferred to a centrifuge tube and centrifuged for 5 min, giving a clear yellow supernatant of approximately 0.5 M concentration. A thick-walled glass reaction vessel with a septum was charged with 5.5 mL (~2.75 mmol) of the ylide solution followed by a solution of 117 mg (0.32 mmol) of (−)-8 in 2.5 mL of THF. The septum was replaced with a rubber stopper, which was wired in place, and the reaction mixture was placed in an 85 °C oil bath and heated overnight. The resulting opaque yellow mixture was diluted with diethyl ether, washed twice with water, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 520.1 mg of a yellow-brown liquid. Purification by preparative TLC (10:1 hexane–diethyl ether) gave 99.4 mg (86%) of (−)-9 as an oil: ^1H NMR (δ, $CDCl_3$) 6.84 (2 H, s), 4.88 (1 H, m), 4.68 (1 H, m), 4.41–4.36 (1 H, m), 4.27–4.20 (1 H, m), 2.4–1.3 (9 H, m), 2.27 (6 H, s), 2.26 (3 H, s), 1.68 (3 H, s), 1.61 (3 H, s), 1.56 (3 H, s), 0.92 (3 H, d, J = 6.65 Hz); IR ($CHCl_3$, cm^{-1}) 1710; HRMS calcd for $C_{25}H_{36}O_2$ m/e 368.2715, found 368.2713; $[\alpha]^{26}_D$ −26.19° (c 0.47, $CHCl_3$).

(5R,10R)-(−)-γ-Methyl-1-(1-methylethenyl)-3-(1-methylethylidene)cyclopentanepropanol (10). A solution of 375 μL (0.375 mmol) of 1.0 M lithium aluminum hydride in diethyl ether at 0 °C was treated dropwise with a solution of 77 mg (0.21 mmol) of (−)-9 in 2.2 mL of diethyl ether. The cold bath was slowly warmed to room temperature, and after being stirred overnight the slightly opaque white mixture was cooled to 0 °C and quenched by slow addition of aqueous saturated Na_2SO_4. The resulting solid was dissolved by addition of 10% H_2SO_4. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 75.5 mg of crude product. Purification by column chromatography (4 g silica, 3:1 hexane–diethyl ether) yielded 38.2 mg (82%) of (−)-10 as a clear, colorless oil: ^1H NMR (δ, $CDCl_3$) 4.90 (1 H, m), 4.70 (1 H, m), 3.77–3.71 (1 H, m), 3.65–3.57 (1 H, m), 1.74 (3 H, s), 1.64 (3 H, s), 1.59 (3 H, s), 0.90 (3 H, d, J = 7.16 Hz), 2.4–1.1 (10 H, m); IR ($CHCl_3$, cm^{-1}) 3600; HRMS calcd for $C_{15}H_{26}O$ m/e 222.1981, found 222.1984; $[\alpha]^{26}_D$ −50.64° (c 0.42, $CHCl_3$).

(5R,10R)-(−)-10-Methyl-6-methylene-2-(1-methylethenyl)spiro[4.5]decan-8-ol (11). To a solution of 1.5 mL (18.5 mmol) of pyridine in 2 mL of CH_2Cl_2 at room temperature was added 200 mg (20 mmol) of chromium trioxide. This mixture was stirred for 20 min, giving a red-orange slurry. A 1.5-mL aliquot of this slurry was transferred to a room temperature solution of 59 mg (0.27 mmol) of (−)-10 in 3.8 mL of CH_2Cl_2, giving an immediate dark brown mixture containing a brown-black precipitate. After being stirred, for 30 min, the reaction mixture was diluted with diethyl ether, filtered through Celite and rinsed, and concentrated in vacuo to afford 68.3 mg of the crude olefinic aldehyde as a brown liquid. This liquid was dissolved in 5 mL of CH_2Cl_2 at room temperature and treated with 150 μL (0.15 mmol) of 1.0 M tin(IV) chloride in methylene chloride. After 5 min at room temperature the reaction was quenched with aqueous saturated ammonium chloride, diluted with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 58.4 mg of crude (−)-11. Purification via column chromatography (10 g of silica, 3:1 hexane–diethyl ether) afforded 34.3 mg (60%) of (−)-11 as a white solid having the same spectral properties as an analytical sample. Recrystallization from pentane afforded a white solid: mp 91–94 °C; ^1H NMR (δ, $CDCl_3$) 4.88 (1 H, m), 4.63 (1 H, m), 3.90 (1 H, m), 1.66 (3 H, s), 1.59 (3 H, s), 2.1–1.1 (10 H, m), 0.88 (3 H, d, J = 7.19 Hz); IR ($CHCl_3$, cm^{-1}) 3580, 3440 (br); $[\alpha]^{27}_D$ −109.7° (c 0.31, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}O$: C, 81.8; H, 10.9. Found: C, 81.66; H, 10.99.

(−)-β-Vetivone (1). A room temperature solution of 139 μL (1.72 mmol) of pyridine in 2.2 mL of CH_2Cl_2 was treated with 85.8 mg (0.86 mmol) of chromium trioxide, giving an orange-red slurry. After the mixture was stirred for 25 min at room temperature, a solution of 31.4 mg (0.14 mmol) of (−)-11 in 1 mL of CH_2Cl_2 was added, giving a brown mixture with a black precipitate. After being stirred for 30 min, the mixture was diluted with diethyl ether and filtered through Celite. The organic layer was washed with 5% HCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 37 mg of crude (−)-β-vetivone. Purification via column chromatography (5:1 hexane–diethyl ether) afforded 18.5 mg (60%) of (−)-β-vetivone as a white solid: mp 33–36 °C; ^1H NMR (δ, $CDCl_3$) 5.78 (1 H, m), 1.88 (3 H, d, J = 1.73 Hz), 1.66 (3 H, s), 1.62 (3 H, s), 0.96 (3 H, d, J = 6.34 Hz), 2.6–1.9 (9 H, m); IR ($CHCl_3$, cm^{-1}) 1655, 1610. A portion (7 mg) of this sample was purified with a chromatotron (2:1 hexane–diethyl ether) to give 5.5 mg of (−)-β-vetivone as a white solid: mp 38–39 °C; $[\alpha]^{24}_D$ −37.11° (c 0.54, EtOH). An authentic sample of (−)-β-vetivone had identical ^1H NMR and IR spectra and mp 37–38 °C; $[\alpha]^{24}_D$ −43.45° (c 0.51, EtOH) [lit.[2c] $[\alpha]_D$ −38.92° (c 10.62, alcohol)].

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Chiral Synthesis of Bicyclomycin and Diastereomeric Stereoselectivity of the Key Aldol Condensation

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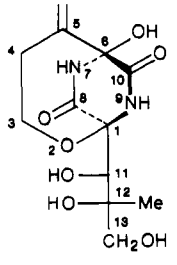
Optically pure bicyclomycin (**1**) was synthesized via aldol condensation of racemic 7,9-bis(*p*-methoxybenzyl)-5-methylene-6-[(*tert*-butyldimethylsilyl)oxy]-7,9-diaza-2-oxabicyclo[4.2.2]decane-8,10-dione (**2**) with 2,3-di-*O*-isopropylidene-2-*C*-methyl-L-glyceraldehyde (**3**). The major condensation product **4** was then N-de(*p*-methoxybenzyl)ated and O-deisopropylidenated simultaneously with CAN and O-de(*tert*-butyldimethylsilyl)ated with Bu_4NF under finely optimized conditions, respectively, to give **1**. The structures of three other diastereomers of **4** were elucidated through comparison with the products of the aldol condensation of optically pure **2** and **3**. The compounds (+)-**2** and (−)-**2** were prepared by diastereomeric separation of the synthetic precursor of **2**, i.e., 5,6-dihydroxy-7,9-bis(*p*-methoxybenzyl)-7,9-diaza-2-oxabicyclo[4.2.2]decane-8,10-dione as its (−)-MTPA ester, followed by the previously established four-step conversion. The stereoselectivity of the aldol condensation was explained by the chair conformation-like transition states.

Bicyclomycin (**1**), an antibiotic isolated from cultures of *Streptomyces sapporonensis*[1] and *S. aizunensis*[2] has unique antibacterial activity[3] against some Gram-negative microorganisms and has been produced by a Japanese pharmaceutical company. The relative[4] and absolute[5] structure of **1** was established by X-ray analysis. The most remarkable structural characteristic of **1** is a highly oxidized, bicyclic 2,5-piperazinedione (BPD) framework, which has prompted many strategies for the total synthesis of **1**. Three groups have reported the synthesis of racemic[6] and chiral (78% ee[7] and 100% ee[8]) bicyclomycin. In this paper, we report the details of the preliminary communication[8] on the chiral synthesis of **1**.

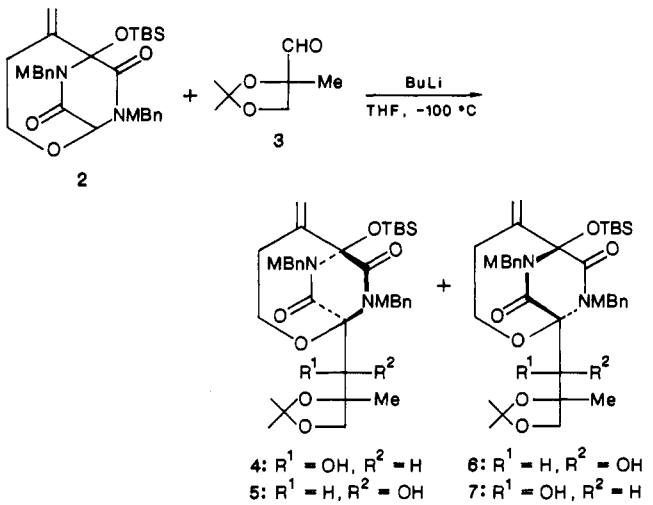


1

Results and Discussion

Aldol Condensation of 2 with 3. In the course of these total syntheses,[6-8] the C–C coupling of the BPD bridgehead carbanion with the branched-chain aldehyde is a common key step. In our synthesis, 7,9-bis(*p*-methoxybenzyl)-5-methylene-6-[(*tert*-butyldimethylsilyl)oxy]-7,9-diaza-2-oxabicyclo[4.2.2]decane-8,10-dione (**2**)[9] was chosen as the BPD derivative and 2,3-di-*O*-isopropylidene-2-*C*-methyl-L-glyceraldehyde (**3**)[10] as the carbonyl component for the

Scheme I



2 **3**

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