New Stereoselective Synthesis of Paeonilactone B

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Abstract: A new stereoselective synthesis of paeonilactone B has been achieved in ten steps and in 11.5% overall yield starting from the enantiomerically enriched terpenol **2**. Key synthetic steps are based on a regioselective metalation and on a regio- and diastereoselective epoxidation.

Key words: natural product, terpene, metalation, homoallylic epoxidation, lactone

Paeony roots (*Paeonia albiflora* Pallas) are largely used in traditional Chinese medicine for the treatment of abdominal pain.[1] In the 1985, the terpenes **1a–c**, called respectively paeonilactone A, B, and C, were identified as the main biological active constituents of this plant (Figure 1).[2]

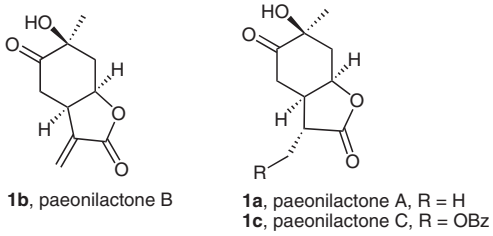
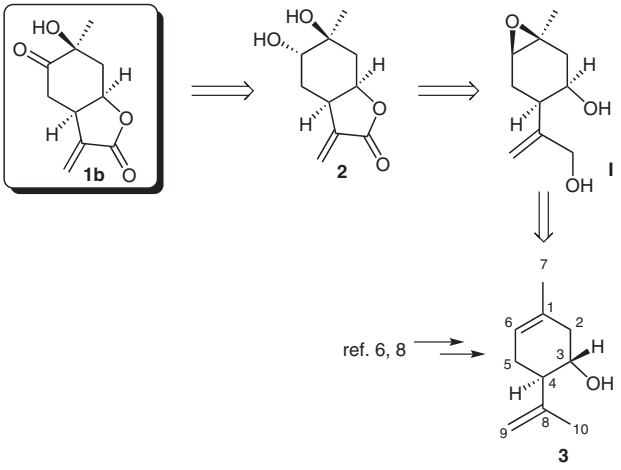


Figure 1

The important biological activity and unique structural complexity of these terpenes have attracted the attention of several organic chemists, who have been challenged by its preparation, either in racemic[3] or in enantiomerically pure form.[4,5] Herein, we present a new stereoselective synthesis of paeonilactone B (**1b**).

Inspection of **1b** reveals three main structural features: (1) a tertiary alcohol α to a ketone, (2) a butanolide lactone *cis*-fused to a six-membered ring, and (3) an exocyclic double bond. Our retrosynthetic analysis led us to envisage **3** as the optimal starting material (Scheme 1).[6] Indeed, **3** bears an isopropenyl and a hydroxy group in favorable positions. Moreover, the latter might assist the formation of the required quaternary stereocenter exploiting the Sharpless epoxidation of chiral homoallylic alcohols.[7] Thus, it is matter of how to introduce functionality at C10 and manipulate it in such a way to prepare the key intermediate **2** on which our strategy is based. Indeed, from such an intermediate we planned to proceed similarly to other reported syntheses.[4a,b]

Recently we have described a new and efficient preparation of the enantiomerically enriched *trans*-terpenol **3** (81% ee) by enzymatic resolution.[8]



Scheme 1 Retrosynthesis of paeonilactone B

The synthesis of **1b** is shown in Scheme 2. First, we regioselectively introduced the hydroxy functionality at C10 by quenching the metalated form of **3**, obtained by treatment with butyllithium and potassium *tert*-butoxide in hexane at room temperature, with fluorodimethoxyborane at –78 °C, and successively with hydrogen peroxide at –50 °C to give diol **4**, as a white solid, in 41% yield after crystallization in hexane–diethyl ether.[9] The crystallization allowed a substantial improvement in the initial enantiomeric excess up to 98% (*vide infra*). The observed complete regioselectivity is likely due to the presence of the hydroxy group, indeed, the metalation of limonene under similar experimental conditions gives a mixture of the two possible regioisomers.[10] Then, we proceeded with the inversion of the C3 stereocenter by a standard oxidation–reduction protocol. However, first we selectively protected the primary hydroxy group with *tert*-butyldiphenylsilyl chloride in *N*,*N*-dimethylformamide and in the presence of imidazole to give **5** in 94% yield. Thus, the alcohol **5** was oxidized with Dess–Martin periodinane in dichloromethane to give the corresponding ketone,[11] which was then reduced with L-Selectride at –78 °C in tetrahydrofuran to give the *cis*-alcohol **6** in 74% yield over two steps. Epoxi-

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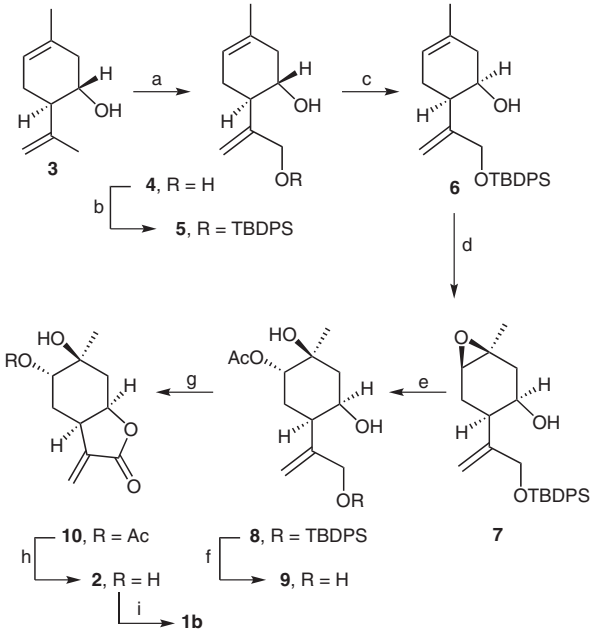
dation of the latter with one stoichiometric equivalent of *tert*-butyl hydroperoxide in the presence of a catalytic amount of vanadyl acetylacetonate, in benzene at room temperature, gave exclusively **7** in 93% yield.[7,12,13] We were quite surprised by the high regioselectivity, because the epoxidation of the exocyclic double bond of (+)-neoisopulegol[12,13] proceeds in high yield under identical experimental conditions.



Scheme 2 Synthesis of the key intermediate **2**. *Reagents and conditions*: (a) 1. BuLi, *t*-BuOK, hexane, 0°C to r.t., 4 h; 2. $(MeO)_2BF$, –78 °C, H_2O_2, –50 °C, 63%; 41% after crystallization; (b) TBDPSCl, imidazole, DMF, r.t., 94%; (c) 1. DMP, CH_2Cl_2; 2. L-Selectride, THF, –78 °C; 78% (2 steps); (d) cat. $VO(acac)_2$, TBHP, benzene, r.t., 93%; (e) NaOAc, AcOH, 50 °C, 78%; (f) TBAF, THF, 95%; (g) $PhI(OAc)_2$, cat. TEMPO, CH_2Cl_2, r.t.; 1 h, 88%; (h) K_2CO_3, MeOH, 68%; (i) IBX, DMSO, 91%.

Next, the epoxide ring was opened by treatment with sodium acetate in acetic acid at 50 °C to give the hydroxy acetate **8** in 78% yield.

At this stage the synthetic sequence was completed by cleavage of the protective silyl group with tetrabutylammonium fluoride in tetrahydrofuran to give **9** in 95% yield, which was then transformed to the lactone **10** by oxidation of the primary alcohol with a catalytic amount of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and (diacetoxyiodo)benzene as co-oxidant in dichloromethane at room temperature in 88% yield.[14] Then, hydrolysis of **10** with potassium carbonate in methanol gave **2** in 68% yield {$[\alpha]_D^{25}$ +30.8 (*c* 1.0, $CHCl_3$) [Lit.[4a] $[\alpha]_D$ +31.6 ($CHCl_3$)]}. Finally, **2** was converted into paeonilactone B (**1b**) by Swern oxidation of the secondary hydroxy group following the previously reported procedure in a modest 37% yield, moreover, the resulting purification was troublesome.[3a,4a,b] Alternatively, oxidation of **2** with 2-iodoxybenzoic acid (IBX)[15] in dimethyl sulfoxide gave **1b** {$[\alpha]_D^{25}$ +22.7 (*c* 0.5, MeOH) [Lit.[2] $[\alpha]_D$ +23.2 (MeOH)]} in 91% yield.

In conclusion we have reported a new and concise stereoselective synthesis of **1b** in ten steps starting from **2**, and in 11.5% overall yield.

^1H NMR and ^{13}C NMR: Bruker AMX 400 (400 MHz); $CDCl_3$ solns at r.t. unless otherwise stated, chemical shifts relative to internal TMS. TLC analyses: Merck Kieselgel 60 F254 plates. All the gravimetric chromatographic columns were carried out using silica gel. All solvents and reagents were purchased from Fluka and were used without any further purification.

(1*S*,6*R*)-6-[1-(Hydroxymethyl)vinyl]-3-methylcyclohex-3-en-1-ol (4)

To a well-stirred soln of BuLi (14. mL, 35.5 mmol) in hexane (20 mL) was added dropwise a soln of **3** (2.7 g, 17.8 mmol) in hexane (5 mL) and *t*-BuOK (2.2 g, 19.6 mmol) at 0 °C to r.t. under an N_2 atmosphere. After 4 h, $(MeO)_2BF$ (8.3 g, 53.3 mmol) was added dropwise at –78 °C, and, after 1 h H_2O_2 (6 mL, 30%) was added at –50 °C over 10 min. After 1 h of vigorous stirring at r.t., the mixture was poured into 1 M NaOH (100 mL) and extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with brine (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography purification (hexane–EtOAc, 7:3) gave, in order of elution, **3** (0.9 g) and **4** (1.9 g, 63%). Upon crystallization (hexane–Et_2O, 9:1), diol **4** (1.3 g, 41%) was obtained as white crystals; mp 110 °C.

$[\alpha]_D^{25}$ +96.1 (*c* 1.0, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.33(m, 1 H), 5.24 (dd, *J* = 1.2, 0.9 Hz, 1 H), 5.08 (br s, 1 H), 4.21–4.07 (m_{AB}, 2 H), 3.81 (ddd, *J* = 10.6, 9.6, 5.6 Hz, 1 H), 2.35 (br s, 1 H), 2.36–2.25 (m, 2 H), 2.20–2.0 (m, 3 H), 1.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 132.0, 120.0, 113.9, 70.2, 64.8, 46.6, 39.1, 31.9, 23.0.

(1*S*,6*R*)-6-{1-[(*tert*-Butyldiphenylsiloxy)methyl]vinyl}-3-methylcyclohex-3-en-1-ol (5)

To a r.t. soln of **4** (0.98 g, 5.8 mmol) and imidazole (0.8 g, 11.6 mmol) in DMF (10 mL) was added TBDPSCl (1.75 g, 1.6 mmol). After complete conversion [TLC (hexane–EtOAc, 8:2)], the mixture was quenched with brine (20 mL) and washed with Et_2O (2 × 50 mL). The combined organic phases were washed with 0.1 M HCl (30 mL) and brine (50 mL). Then, the organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give crude material, which was purified by column chromatography (hexane–EtOAc, 9:1) to give **5** (2.2 g, 94%) as yellow oil.

$[\alpha]_D^{25}$ +34.1 (*c* 1.2, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.71 (m, 4 H), 7.48–7.39 (m, 6 H), 5.37 (d, *J* = 1.6 Hz, 1 H), 5.31 (m, 1 H), 5.12 (br s, 1 H), 4.24–4.11 (m_{AB}, 2 H), 3.90 (ddd, *J* = 10.6, 9.6, 5.6 Hz, 1 H), 2.58 (br s, 1 H), 2.36 (m, 1 H), 2.25 (dt, *J* = 10.4, 5.4 Hz, 1 H), 2.12–2.01 (m, 3 H), 1.69 (s, 3 H), 1.12 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 135.6, 133.1, 132.2, 129.8, 127.7, 119.9, 113.0, 69.6, 66.0, 46.7, 38.7, 31.8, 26.8, 23.0, 19.1.

(1*R*,6*R*)-6-{1-[(*tert*-Butyldiphenylsiloxy)methyl]vinyl}-3-methylcyclohex-3-en-1-ol (6)

To a soln of **5** (1.9 g, 4.7 mmol) in CH_2Cl_2 (10 mL) was added DMP (2.2 g, 5.2 mmol). After complete conversion [TLC (hexane–EtOAc, 8:2)], the mixture was quenched with sat. Na_2SO_3 soln (20 mL) and sat. $NaHCO_3$ soln (20 mL) and washed with Et_2O (2 × 50 mL). The combined organic phases were washed with 0.1 M HCl

(30 mL) and brine (50 mL). Then, the organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give crude material, which was of sufficient purity for the next step. Thus, to a soln of the ketone in THF (20 mL) was added dropwise 1 M L-Selectride in THF (6 mL) at –78 °C over 10 min under an N_2 atmosphere. After complete conversion (TLC), the mixture was quenched with sat. NH_4Cl soln (30 mL) and washed with Et_2O (2 × 50 mL). The combined organic phases were washed with brine (50 mL). Then, the organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give crude material. Column chromatography purification (hexane–Et_2O, 9:1) gave **6** (1.4 g, 74%).

$[\alpha]_D^{25}$ –4.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.73 (m, 4 H), 7.47–7.41 (m, 6 H), 5.48 (m, 1 H), 5.27 (m, 1 H), 5.09 (br s, 1 H), 4.28–4.17 (m_{AB}, 2 H), 4.05 (m, 1 H), 2.40–2.25 (m, 3 H), 2.17–1.95 (m, 2 H), 1.69 (m, 4 H), 1.10 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 135.5, 133.2, 130.3 129.7, 127.7, 120.0, 111.9, 66.9, 66.4, 41.6, 40.0, 26.8, 24.9, 23.3, 19.1.

(1*R*,2*R*,4*R*,5*S*)-2-{1-[(*tert*-Butyldiphenylsiloxy)methyl]vinyl}-4,5-epoxy-5-methylcyclohexan-1-ol (7)

To a well stirred soln of **6** (1.30 g, 3.2 mmol) in benzene (20 mL) was added a soln of TBHP in toluene (6.6 mL, 3.23 mmol) and a catalytic amount of $VO(acac)_2$. After 10 h, the mixture was diluted with Et_2O and washed with brine (30 mL).The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Column chromatography purification (silica gel, hexane–EtOAc, 7:3) afforded **7** (1.26 g, 93%) as an oil.

$[\alpha]_D^{25}$ +3.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.65 (m, 4 H), 7.32–7.50 (m, 6 H), 5.26 (br s, 1 H), 5.07 (br s, 1 H), 4.21–4.07 (m_{AB}, 2 H), 3.82 (ddd, *J* = 10.6, 9.6, 5.6 Hz, 1 H), 3.13 (m, 2 H), 2.28 (dd, *J* = 2.6, 15.4 Hz, 1 H), 2.16–2.00 (m, 3 H), 1.88 (dd, *J* = 3.9, 15.4 Hz, 1 H), 1.33 (s, 3 H), 1.08 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 135.5, 133.5, 129.9, 127.9, 111.1, 68.0, 66.6, 60.2, 59.8, 39.8, 37.4, 27.1, 25.2, 23.2, 19.5.

(1*S*,3*R*,4*R*,6*S*)-6-Acetoxy-4-{1-[(*tert*-butyldiphenylsiloxy)methyl]vinyl}-1-methylcyclohexane-1,3-diol (8)

A soln of **7** (1.2 g, 2.8 mmol) and NaOAc (1.0 g, 12.2 mmol) in AcOH (10 mL) was heated at 50 °C for 3 h. Then, the mixture was poured in brine (20 mL) and washed with Et_2O (4 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4) and the solvent was removed under reduced pressure. Column chromatography purification (silica gel, hexane–EtOAc, 2:8) afforded **8** (1.07 g, 78%) as an oil.

$[\alpha]_D^{2}$ +18.3 (*c* 0.7, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.65 (m, 4 H), 7.32–7.50 (m, 6 H), 5.26 (br s, 1 H), 5.02 (br s, 1 H), 4.89 (br s, 1 H), 4.66 (br s, 1 H), 4.21–4.07 (m_{AB}, 2 H), 4.01 (br s, 1 H), 3.03 (br s, 1 H), 2.57 (br d, *J* = 13.5 Hz, 1 H), 2.38 (dt, *J* = 14.5, 2.6 Hz, 1 H), 2.03 (s, 3 H), 1.98 (br d, *J* = 14.5 Hz, 1 H), 1.79 (dd, *J* = 14.8, 2.6 Hz, 1 H), 1.64 (dt, *J* = 14.1, 2.9 Hz, 1 H), 1.12 (s, 3 H), 1.06 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 148.6, 135.5, 132.8, 129.9, 127.9, 127.8, 114.2, 75.6, 70.1, 68.9, 66.1, 39.1, 37.8, 26.7, 26.0, 24.0, 21.2, 19.1.

(1*S*,3*R*,4*R*,6*S*)-6-Acetoxy-4-[1-(hydroxymethyl)vinyl]-1-methylcyclohexane-1,3-diol (9)

To a soln of **8** (1.20 g, 2.6 mmol) in THF (10 mL) was added TBAF (1.0 g, 3.2 mmol). After 1 h the mixture was concentrated under reduced pressure to give crude material. Column chromatography purification (silica gel, EtOAc) afforded **9** (0.60 g, 95%) as an oil.

$[\alpha]_D^{25}$ +30.4 (*c* 1.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.21 (s, 1 H), 5.05 (s, 1 H), 4.87 (m, 1 H), 4.81 (br s, 1 H), 4.15–4.07 (m, 4 H), 2.57 (br d, *J* = 13.5 Hz, 1 H), 2.38 (dt, *J* = 14.5, 2.6 Hz, 1 H), 2.08 (s, 3 H), 1.95 (br d, *J* = 14.5 Hz, 1 H), 1.84 (dd, *J* = 14.8, 2.6 Hz, 1 H), 1.65 (dt, *J* = 14.1, 2.9 Hz, 1 H), 1.12 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 148.6, 115.6, 75.3, 70.6, 70.0, 64.5, 40.5, 38.1, 26.1, 24.2, 21.3.

(3a*R*,5*S*,6*S*,7a*R*)-5-Acetoxy-6-hydroxy-6-methyl-3-methylenehexahydrobenzofuran-2(3*H*)-one (10)

A soln of **9** (0.50 g, 2.0 mmol) in CH_2Cl_2 (10 mL) was treated with $PhI(OAc)_2$ (2.1 g, 6.5 mmol) and TEMPO (0.1 g) and stirred at r.t. until no **9** was detected by TLC (1 h). The mixture was poured into ice (50 g) and washed with 0.5 M Na_2SO_3 (50 mL) and extracted with Et_2O (2 × 50 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Column chromatography purification (silica gel, EtOAc) afforded **10** (0.43 g, 88%) as an oil.

$[\alpha]_D^{25}$ +69.1 (*c* 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (d, *J* = 1.9 Hz, 1 H), 5.64 (d, *J* = 1.9 Hz, 1 H), 4.78 (dd, *J* = 3.6, 6.6 Hz, 1 H), 4.63 (dd, *J* = 5.6, 11.3 Hz, 1 H), 3.14 (br dd, *J* = 6.6, 13.1 Hz, 1 H), 2.21–2.00 (m, 5 H), 1.92–1.84 (m, 2 H), 1.22 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 169.6, 138.6, 121.2, 75.6, 73.7, 69.2, 37.9, 36.6, 27.0, 23.7, 21.0.

(3a*R*,5*S*,6*S*,7a*R*)-5,6-Dihydroxy-6-methyl-3-methylenehexahydrobenzofuran-2(3*H*)-one (2)

An ice-cold mixture of **10** (0.35 g, 1.44 mmol) and K_2CO_3 (0.40 g, 2.9 mmol) in MeOH (10 mL) was left to reach r.t., and, after complete conversion (TLC), the mixture was concentrated under reduced pressure without heating. The moisture was then diluted in CH_2Cl_2 (50 mL) and washed with brine (20 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Column chromatography purification (silica gel, EtOAc) afforded **2** (0.19 g, 68%) as a white solid.

$[\alpha]_D^{25}$ +30.8 (*c* 1.0, $CHCl_3$) {Lit.[4a] $[\alpha]_D$ +31.6 ($CHCl_3$)}.

^{1}H NMR spectral data are consistent with those previously reported.[4a]

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 138.3, 121.1, 74.2, 73.8, 68.6, 37.1, 36.6, 23.8, 21.2.

Paeonilactone B (1b)

A soln of **2** (0.10 g, 0.50 mmol) and IBX (0.28 g, 1.0 mmol) in DMSO (5 mL) was stirred at r.t. for 3 h. Then the mixture was quenched with ice (10 g) and brine (10 mL), and washed with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Column chromatography purification (silica gel, EtOAc–hexane, 7:3) afforded **1b** (0.09 g, 91%) as a white solid.

$[\alpha]_D^{25}$ +22.7 (*c* 0.6, MeOH) {Lit.[2] $[\alpha]_D$ +23.2 (MeOH)}.

^{1}H and ^{13}C NMR spectral data are consistent with those previously reported.[2]

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