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Total Syntheses of (+)-Paeonilactone B and (–)-Paeonisuffrone

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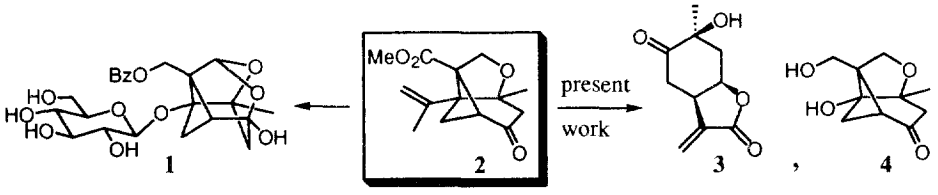
Abstract: A novel synthesis of (+)-paeonilactone B, a minor constituent of Paeoniae Radix, and the first synthesis of (–)-paeonisuffrone, a new monoterpene recently isolated from Moutan Cortex, have been accomplished from the tricyclic compound which functioned well as a key synthetic intermediate in our previous synthesis of (–)-paeoniflorin.

In the course of synthetic studies[1] on pharmacologically active principles of Paeoniae Radix (the root of *Paeonia albiflora* Pallas), we have recently achieved a total synthesis of (–)-paeoniflorin (**1**) utilizing the tricyclic ketone **2** as a key synthetic intermediate.[2] In order to see if this tricyclic ketone **2** can also serve as a common pivotal synthetic precursor of other types of monoterpenes biogenetically related to paeoniflorin (**1**), we undertook further investigation on the syntheses of (+)-paeonilactone B (**3**),[3] a minor constituent of Paeoniae Radix, and (–)-paeonisuffrone (**4**),[4] a new monoterpene isolated from Moutan Cortex (the root of *Paeonia suffruticosa* Andrews), from **2**. These monoterpenes are available only in small quantities from the corresponding crude drugs and, therefore, their efficient syntheses are required to make their pharmacological study possible. Herein we now wish to report a novel synthesis[1b,5] of (+)-paeonilactone B (**3**) and the first synthesis of (–)-paeonisuffrone (**4**).

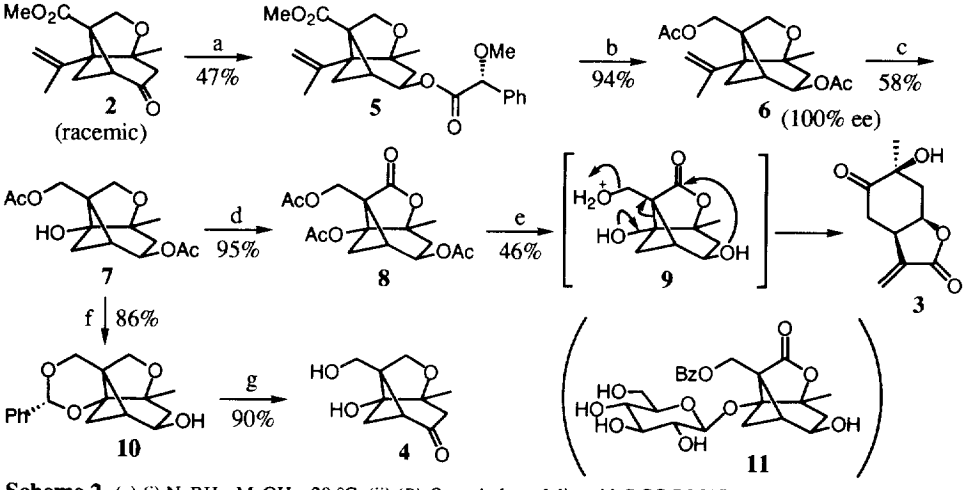


Scheme 1

The racemic tricyclic ketone **2** was first converted to optically pure diacetate **6**, $[\alpha]_D^{32}$ –28.2° (*c* 1.27, $CHCl_3$), *via* O-methylmandelate **5**, $[\alpha]_D^{28}$ –63.1° (*c* 1.00, $CHCl_3$), in 44% overall yield according to the previously developed method.[2] Reaction of **6** with ozone followed by *p*-nitrobenzoylation brought about Criegee rearrangement[6] of the resulting peroxy ester to give alcohol **7**, $[\alpha]_D^{30}$ +25.8° (*c* 1.95, $CHCl_3$), in 58% yield together with 20% yield of the methyl ketone produced by ozonolysis of **6**. After acetylation of **7**, RuO_4 oxidation[7] of the corresponding triacetate, $[\alpha]_D^{27}$ –25.5° (*c* 0.44, MeOH), proceeded very cleanly to afford lactone **8**, $[\alpha]_D^{27}$ +16.0° (*c* 0.62, MeOH), in 95% overall yield. Upon treatment of the lactone **8** with 4% methanolic HCl at room temperature, acid catalyzed skeletal rearrangement occurred as in **9** to furnish (+)-paeonilactone B (**3**) although the yield was moderate (46%). Interestingly, this type of reaction might intervene

in the metabolic process of albiflorin (**11**) to paeonilactones by human intestinal bacteria.[8] The synthetic substance, $[\alpha]_D^{27}$ +27.3° (*c* 0.06, MeOH), was identical with previously prepared authentic sample,[1b] $[\alpha]_D^{27}$ +24.9° (*c* 1.16, MeOH), by spectroscopic (^{1}H NMR, IR, MS) and chromatographic comparisons.

The synthesis of (–)-paeonisuffrone (**4**) has also been accomplished by a four step sequence from the alcohol **7** as follows. Treatment of **7** with methanolic NaOMe followed by benzylidene acetalization afforded benzylidene acetal **10**, $[\alpha]_D^{30}$ –2.7° (*c* 0.84, $CHCl_3$), in 86% overall yield. Swern oxidation of **10** followed by hydrogenolytic deprotection produced (–)-paeonisuffrone (**4**) in 90% overall yield. The spectral data (^{1}H and ^{13}C NMR, IR, MS) of the synthetic substance, mp 144-144.5 °C (hexane-AcOEt), were identical with those of natural paeonisuffrone,[4] although there was discrepancy in the specific rotation, synthetic: $[\alpha]_D^{30}$ –70.1° (*c* 1.29, MeOH); natural: $[\alpha]_D$ –16.8° (*c* 1.5, MeOH). As a result, the present synthesis made the absolute structure of natural paeonisuffrone unambiguous.[9]



Scheme 2. (a) (i) $NaBH_4$, MeOH, –20 °C, (ii) (*R*)-O-methylmandelic acid, DCC-DMAP (catalyst), then separation by SiO_2 column chromatography; (b) (i) $LiAlH_4$, THF, (ii) Ac_2O, pyridine-DMAP (catalyst); (c) O_3, MeOH, –78 °C, then *p*-NO_2-C_6H_4COCl, Et_3N-DMAP (catalyst), CH_2Cl_2; (d) (i) Ac_2O, pyridine-DMAP (catalyst), (ii) $RuCl_3$ (0.45 equiv), $NaIO_4$ (20 equiv), CCl_4-MeCN-0.05 M phosphate buffer (1:1:1.5), 50 °C; (e) 4% HCl-MeOH; (f) (i) NaOMe, MeOH, (ii) PhCHO, *p*-TsOH-H_2O (catalyst), benzene, reflux; (g) (i) $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C and then Et_3N, (ii) H_2, $Pd(OH)_2$, MeOH-AcOEt-H_2O (6:6:1).

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9. The absolute structure has been tentatively determined by modified Mosher's method.[4]

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