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A Facile Synthesis of (+)-Ramulosin

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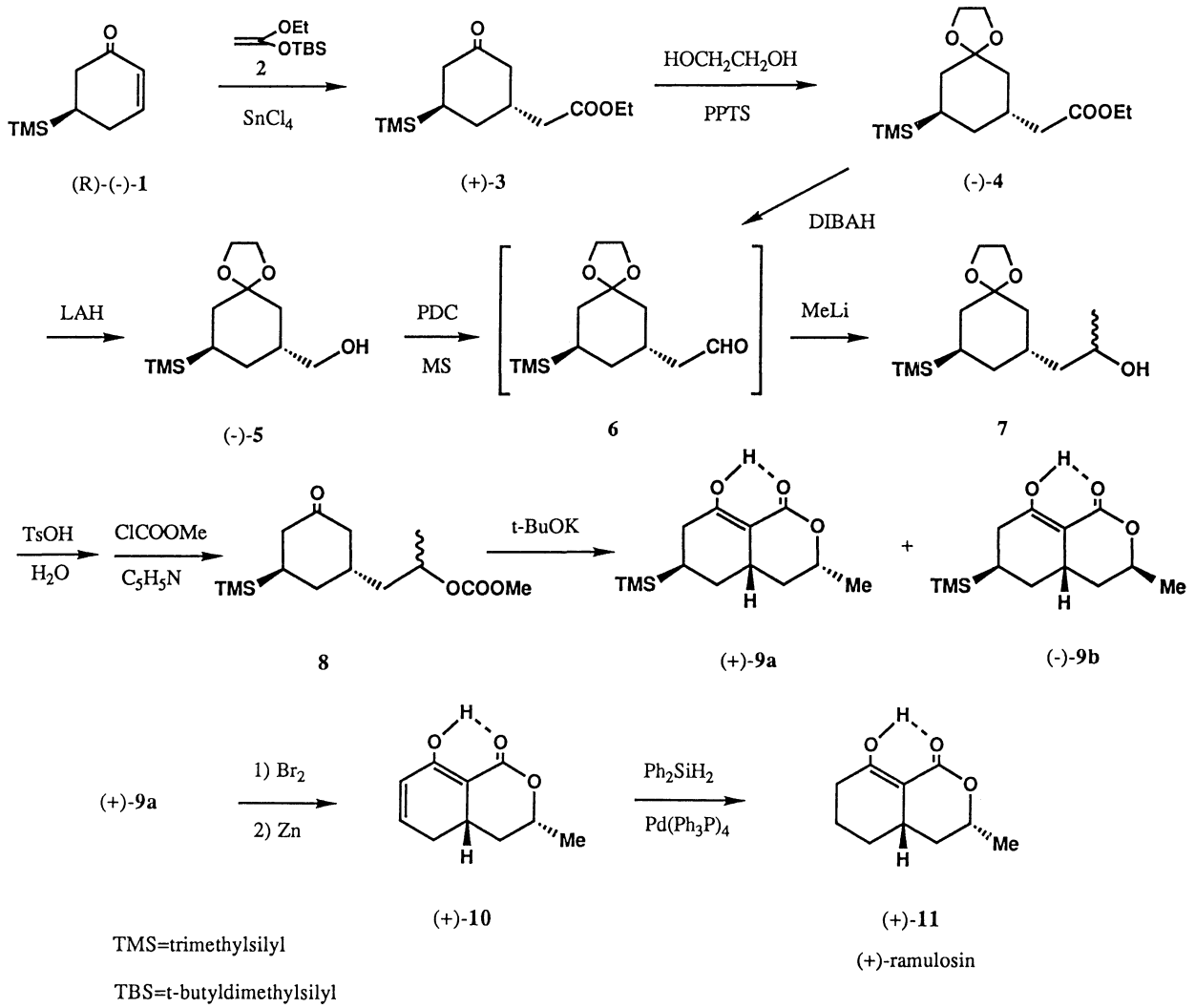
The title compound was synthesized from (R)-(-)-5-trimethylsilyl-2-cyclohexenone.

(+)-Ramulosin [(+)-**11**] was isolated from Pestalotia ramulosa, and it inhibits germination of seeds and spores of microorganisms.[1] Three racemic and only one enantioselective syntheses of **11** have been reported.[2] Here we wish to report an alternative synthesis of (+)-ramulosin. The key tactical element of the approach involves stereospecific 1,4-addition of acetic ester unit to optically pure 5-trimethylsilyl-2-cyclohexenone (**1**).[3]

Lewis acid catalyzed reaction of silyl ketene acetal (**2**) with (R)-(-)-**1** proceeded smoothly (2 equiv. $SnCl_4$, CH_2Cl_2, -78 °C, 10 min) in a diastereoselective manner to give the corresponding trans-adduct (+)-**3** [$[\alpha]_D^{20}$+72.8°(c 1.76, $CHCl_3$)] as a single isomer in 87% yield. Protection of carbonyl group under usual conditions gave the acetal derivative (-)-**4** [$[\alpha]_D^{21}$-22.28°(c 2.97, $CHCl_3$)] in 82% yield. Reduction with lithium aluminium hydride (LAH) followed by oxidation with pyridinium dichromate (PDC) in the presence of ground molecular sieves and subsequent reaction with methyllithium (THF, -78 °C, 5 min) gave the desired secondary alcohol **7** [61% overall yield from (-)-**4**] as an inseparable mixture of diastereoisomers (ca. 1:1).[4] Synthesis of **7** via direct conversion of the ester (-)-**4** to the aldehyde **6** by DIBAH reduction also gave **7** in 45-56% yields, however, the method lacked reproducibility. Deprotection of the carbonyl group of **7** and subsequent esterification with methyl chloroformate (PyH-CH_2Cl_2, 0 °C, 2 h) gave the diastereomeric carbonate **8** (82%), which were also chromatographically inseparable. Intramolecular cyclization of the carbonate to bicyclic lactone **9a** and **9b** was successfully carried out with potassium t-butoxide (THF, rt, 45 min). At this stage, the desired lactone (+)-**9a** [36%, $[\alpha]_D^{20}$+66.74° (c 2.69, $CHCl_3$), mp 87-88 °C] and its diastereomer (-)-**9b** [47%, $[\alpha]_D^{20}$-13.78° (c 1.95, $CHCl_3$), mp 45-46.5 °C] were easily isolated by column chromatography on silica gel. Treatment of **9a** with 2.5 equivalents of bromine and subsequent reductive dehalogenation with zinc in refluxing ethanol for 20 min gave dehydroramulosin (+)-**10** [$[\alpha]_D^{21}$+115.5°(c 1.67, $CHCl_3$), mp 82-83.5 °C] in 52% yield. Conjugate reduction of (+)-**10** by the reported method[2c] gave (+)-ramulosin [$[\alpha]_D^{22}$+17.1°(c 0.56, EtOH), mp 117.5-118.5 °C, lit.[2a] $[\alpha]_D^{22}$+18.3°(c 1.20, EtOH), mp 118-119 °C] in 56% yield.[5]



(R)-(-)-1 (+)-3 (-)-4

(-)-5 6 7

8 (+)-9a (-)-9b

(+)-9a (+)-10 (+)-11

(+)-ramulosin

TMS=trimethylsilyl

TBS=t-butyldimethylsilyl

Scheme 1.

References

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4) Reaction of triisopropoxymethyltitanium with the aldehyde **6** resulted in a predominant formation of undesired diastereoisomer of **7**.

5) Satisfactory IR and NMR spectra and CH analyses were obtained for all compounds depicted in Scheme 1 (except **6**).

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