A Short Synthesis of (+)-Bakuchiol

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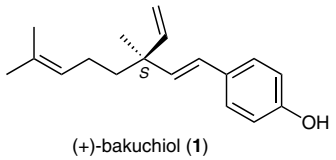
Abstract: The concise enantioselective total synthesis of (+)-bakuchiol has been achieved using an asymmetric 1,4-addition to construct its all-carbon chiral quaternary center based on the induction of chirality by the (2′*S*)-2′-phenyloxazolidinone auxiliary, followed by a one-pot transformation under aldol reaction conditions. The synthesis was completed in four steps from (*E*)-geranic acid in an overall yield of 53%.

Key words: bakuchiol, asymmetric 1,4-addition reaction, asymmetric aldol reaction, removal of oxazolidinone, decarboxylation, all-carbon quaternary center

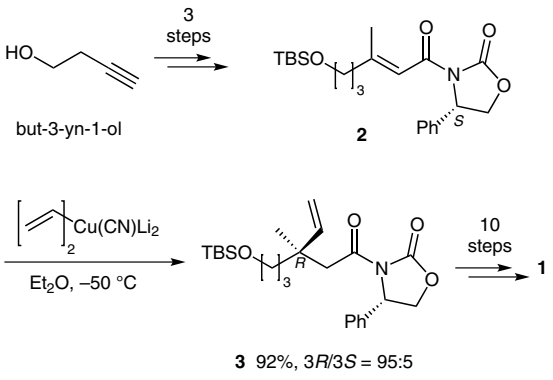
(+)-Bakuchiol (**1**) is a phenolic isoprenoid with a chiral tetraalkylated (all-carbon) quaternary center that was isolated from the seeds of *Psoralea corylifolia* Linn. (Sanskrit: *Bakuchi, Sungandha kantak*; Hindi: *Babchi*) by Dev et al.[1,2] Its plane structure was elucidated in 1966[1,2] and the absolute configuration of its quaternary center was determined to be *S* in 1973[3] (Figure 1).



(+)-bakuchiol (**1**)

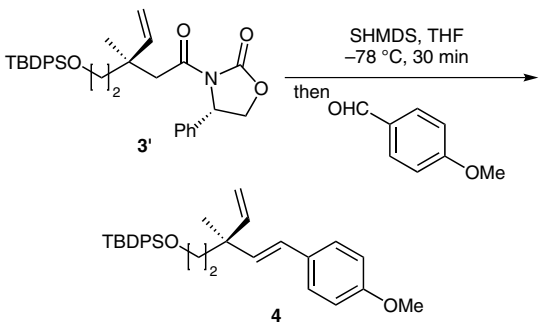
Figure 1 Structure of (+)-bakuchiol (**1**)

(+)-Bakuchiol (**1**), which was initially used as an antibiotic against *Staphylococcus aureus*,[2] has shown a broad range of biological activities against a variety of different targets, such as protein tyrosine phosphatase 1B (PTB1B) inhibition,[4] a caspase-3-dependent apoptosis-inducing effect,[5] prevention of mitochondrial lipid peroxidation,[6] inhibition of inducible nitric oxide synthase (i.e., iNOS and NOS II) expression,[7] and DNA polymerase and topoisomerase II inhibition.[8] Thus, **1** has been recognized as an important lead compound for the development of new medicines. Compound **1** has also become an attractive target for many synthetic chemists because of its biological profile and simple intriguing structure. The first total synthesis of (±)-**1** was achieved by Carnduff and Miller[9] with a Claisen rearrangement being used as a key step in the synthesis. In the 20 years following its isolation, however, there were no reports in the literature concerning the enantioselective total synthesis of **1** because of the difficulties associated with constructing its chiral tetraalkylated quaternary center in a stereoselective manner. Takano et al.[10] reported the first enantiocontrolled total synthesis of (+)-bakuchiol (**1**) in 1990 in 11 steps from (*S*)-*O*-benzylglycidol. Following on from this work, Asaoka et al.[11] (16 steps, in 1999), Li et al.[12] (10 steps, in 2008), Novikov et al.[13] (10 steps, in 2009) and Hoveyda et al.[14] (3 steps, in 2010) have all succeeded in developing elegant enantioselective total syntheses of (+)-**1**. In our previous paper,[15] we reported the successful total synthesis of (+)-bakuchiol (**1**) in 14 steps from but-3-yn-1-ol based on the asymmetric 1,4-addition reaction of $(H_2C{=}CH)_2Cu(CN)Li_2$ to an α,β-unsaturated carboxylic acid derivative equipped with a chiral oxazolidinone auxiliary **2** for constructing the all-carbon chiral quaternary center[15] (Scheme 1).



Scheme 1 Previous total synthesis of (+)-bakuchiol by our group

We recently found that the reaction of **3′** with an electron-rich aromatic aldehyde such as *p*-methoxybenzaldehyde led to the occurrence of a series of reactions, including an aldol reaction followed by the removal of the oxazolidinone moiety through a lactonization/decarboxylation se-



Scheme 2 Sequential one-pot transformation (aldol/β-lactonization/decarboxylation)

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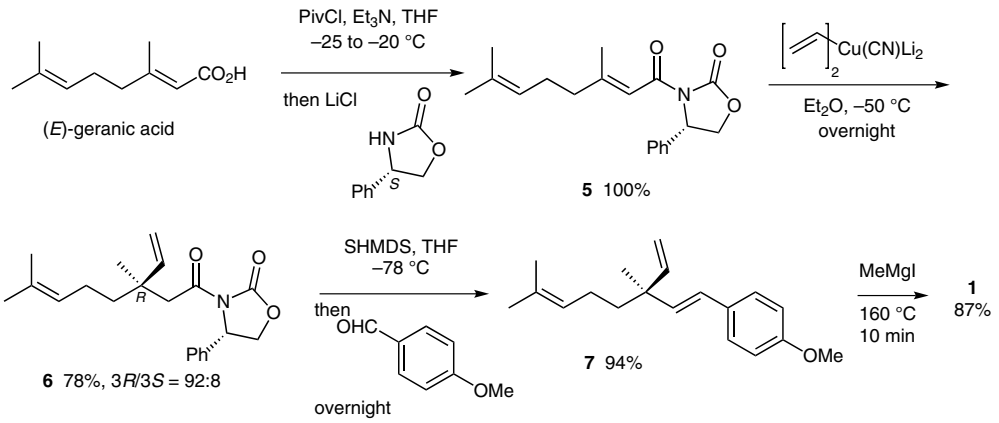

Scheme 3 Total synthesis of (+)-bakuchiol

quence to afford (*E*)-arylalkene **4** in good yield[16] (Scheme 2). This result prompted us to synthesize (+)-bakuchiol (**1**) according to a more efficient route than those previously reported in the literature. Herein, we report a short enantioselective total synthesis of (+)-bakuchiol (**1**) using an asymmetric 1,4-addition to an α,β-unsaturated carboxylic acid derivative equipped with a chiral oxazolidinone auxiliary followed by a sequential one-pot transformation (aldol/β-lactonization/decarboxylation) as the key steps.

Our current synthesis of (+)-bakuchiol (**1**) started from (*E*)-geranic acid (Scheme 3). Thus, (*E*)-geranic acid was treated with a mixture of pivaloyl chloride and triethylamine in THF, followed by a mixture of (2′*R*)-2′-phenyloxazolidinone in the presence of LiCl to give the 1,4-addition precursor **5** in quantitative yield. Compound **5** was then subjected to an asymmetric 1,4-addition reaction with $(H_2C{=}CH)_2Cu(CN)Li_2$ in Et_2O, according to the method described in our previous report.[15] The reaction proceeded smoothly to afford the (*R*)-1,4-adduct **6** in good yield with a diastereoselectivity of 92:8.[17] The one-pot transformation of **6** into *O*-methylbakuchiol (**7**) was then investigated. Thus, the treatment of **6** with SHMDS in THF at –78 °C followed by the addition of *p*-methoxybenzaldehyde led to the occurrence of a domino reaction to give the desired *O*-methylbakuchiol (**7**) in excellent yield. In addition, the (2′*S*)-2′-phenyloxazolidinone generated during this stage was readily recovered in a quantitative manner by silica gel column chromatography. Compound **7** was then demethylated by heating at 160 °C in the presence of MeMgI[9] to give (+)-bakuchiol (**1**) in good yield. The spectral data (^{1}H NMR, ^{13}C NMR, IR, EI–MS, $[\alpha]_D$)[18] collected for the synthetic **1** were identical to those of the natural product.

In conclusion, we have successfully achieved a short and efficient enantioselective total synthesis of (+)-bakuchiol (**1**) in four steps from (*E*)-geranic acid in an overall yield of 64%. This achievement demonstrates that asymmetric 1,4-addition reaction followed by the domino reaction under aldol reaction conditions is effectively applicable to the synthesis of the various compounds including the chiral tetraalkylated quaternary center adjacent to arylated (*E*)-olefin.

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(17) The ratio was determined by ^{1}H NMR (600 MHz).

(18) **Data for Synthetic (+)-Bakuchiol**: $[\alpha]_D^{20}$ +26.0 (*c* 0.45, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.4 Hz, 2 H), 6.77 (d, *J* = 8.4 Hz, 2 H), 6.25 (d, *J* = 16.4 Hz, 1 H), 6.10 (d, *J* = 16.4 Hz, 1 H), 5.88 (dd, *J* = 10.8, 17.2 Hz, 1 H), 5.10 (quint t, *J* = 1.6, 7.2 Hz, 1 H), 5.03 (dd, *J* = 1.6, 10.8 Hz, 1 H), 5.01 (dd, *J* = 1.6, 17.2 Hz, 1 H), 4.78 (br s, 1 H), 1.95 (dt, *J* = 7.2, 9.2 Hz, 2 H), 1.67 (d, *J* = 1.2 Hz, 3 H), 1.58 (d, *J* = 0.8 Hz, 3 H), 1.49 (m, 2 H), 1.19 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 146.5, 136.5, 131.9, 131.5, 127.9, 127.0, 125.4, 115.9, 112.5, 43.1, 41.9, 26.3, 23.9, 23.8, 18.2. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{24}O$: 256.1821; found: 256.1827.