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Betuligenol derivative with growth inhibition and antifeedant activity☆

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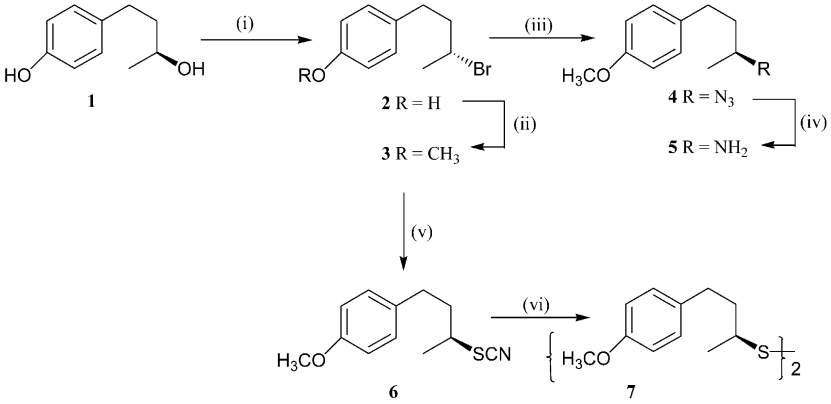
Abstract—The title chiral amine, 3-(4-methoxyphenyl)-1-methylpropylamine **5** has been synthesized from naturally abundant betuligenol **1** in three steps and also in good yield. Furthermore, the versatile intermediate **3** could be manipulated for the preparation of chiral disulphide **7**. The amine derivative **5** prepared from (−)-betuligenol showed significant growth inhibition and antifeedant activity.

We have been working[1–5] on different parts of *Taxus wallichiana* collected from different parts of India for the isolation of paclitaxel = (taxol®), its important analogues and precursor 10-deacetyl baccatin III. During the course of this investigation, we have isolated a major compound from the leaves of *Taxus wallichiana* collected from Kashmir, India, which was identified as (+)-betuligenol **1**.[6] We have also isolated (−)-betuloside and its aglycone (−)-betuligenol from the leaves of the same plant collected from Himachal Pradesh, India. The absolute configuration at the chiral centre in the aglycone portion of (−)-betuloside has been found to be *R* by X-ray diffraction studies.[7] As **1** could be isolated with a yield of 0.2–0.4% from the leaves of *T. wallichiana* and its chemistry has never been studied; we have studied its chemistry to prepare some of its interesting derivatives for potential biological activity.

The reaction of (+)-betuligenol **1**, $[\alpha]_D^{23}$ +16° (*c* 1, MeOH), with 48% HBr at 80 °C cleanly produced its phenolic bromo derivative **2** with a yield of 70%. The above derivative **2** was then converted into its methyl ether **3** with dimethyl sulphate in refluxing acetone. As depicted in Scheme 1, the derivative **3** was found to be a



Scheme 1. Reagents and conditions: (i) HBr (48% aq.), 80 °C, 6 h, 70%; (ii) Me_2SO_4, K_2CO_3, acetone, reflux, 4 h, 85%; (iii) NaN_3, DMF, 70 °C, 6 h, 80%; (iv) Pd–C (10%), EtOH, H2, rt, overnight, 80%; (v) KSCN, DMF, 60 °C, 4 h, 75%; (vi) LAH, THF, reflux, 8 h, 70%.

Keywords: *Taxus wallichiana*; Betuligenol; Chiral amine; Synthesis; Antifeedant activity.
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versatile intermediate as it can be manipulated for the preparation of both chiral amine **5** and disulphide **7** analogues of (+)-betuligenol **1** in good yields.

The bromo derivative **3** was converted into the chiral amine **5** in a two steps reaction sequence which includes reaction of **3** with sodium azide in DMF at 60 °C to form the azide **4** in 85% yield which was then converted into the amine **5** through catalytic hydrogenation in presence of Pd/C in an excellent yield.

Following another sequence of reactions the same reactive bromo intermediate **3** was converted into a disulphide **7** by first treating it with potassium thiocyanate to form the thiocyanate compound **6** which was then reduced with $LiAlH_4$ at 60 °C to form the disulphide **7** in 70% yield. The $LiAlH_4$ reduction of the thiocyanate **6** under the reaction condition directly gave the disulphide **7** instead of a thiol (SH) product as evidenced by mass spectral data. Also, the $LiAlH_4$ reduction product of thiocyanate **6** remained unchanged under the condition of disulphide formation in presence of iodine.[8]

It is worth mentioning that we have also isolated[9] the (−)-betuligenol which is the optical isomer of (+)-betuligenol **1** from the needles of *T. wallichiana*. (−)-Betuligenol has also been converted into amorphous solid, (+)-(*R*)-3-(4-methoxyphenyl)-1-methylpropylamine, $[\alpha]_D^{23}$ +8.0° (*c* 1, MeOH) following the same sequence of reactions as described in Scheme 1.

(−)-Betuligenol was not found to be active in bioassay studies as a growth inhibitor or an antifeedant. But the amine derivative (*R*)-**5** prepared from (−)-betuligenol showed significant activity as a growth inhibitor and antifeedant against 4th instar larvae of *Spilarctia obliqua* Walker (Bihar hairy caterpillar) (Table 1). This insect attacks more than twenty cash crops like lentil, mint and coleus etc.[10–14] In conclusion, we have developed a synthetic sequence through which both the chiral precursors of dobutamine, that is, (*S*)- as well as (*R*)-3-(4-methoxyphenyl)-1-methylpropylamine **5** could be readily synthesized from the naturally abundant (+)-betuligenol **1** as well as (−)-betuligenol in good yield. Further, we have demonstrated the versatility of intermediate **3** as it can easily be manipulated for the synthesis of both chiral amine **5** and disulphide **7** analogues of betuligenol.

Table 1.

Compd	Concentration (ppm)	% Feeding deterrency	% Growth inhibition
(*R*)-**5**	1000	32.0	48.0
	2000	40.0	59.0
	3000	64.0	72.0
	4000	82.0	100.0
	5000	100.0	128.0
Azadirachtin	1000	100.0	—
Diflubenzuron	5	—	100.0

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12. *Selected physical data*: **3**: colourless oil, $[\alpha]_D^{23}$ −8.40° (*c* 1, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.1 Hz, 2H, Ar*H*), 6.82 (d, *J* = 8.1 Hz, 2H, Ar*H*), 4.04 (m, 1H, H-2), 3.77 (s, 3H, OCH_3), 2.75 (m, 2H, H-4), 2.01 (m, 2H, H-3), 1.71 (d, *J* = 6.6 Hz, 3H, 1-CH_3), EI–MS *m*/*z* 242 (M^+), 244 ($M^+ + 2$); **4**: colourless oil, $[\alpha]_D^{23}$ −1.30° (*c* 1, MeOH), IR (Neat, cm^{-1}) 2101, 1613, 1513, 1461, 1247, 1179, 1037, 928, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 7.7 Hz, 2H, Ar*H*), 6.83 (d, *J* = 7.1 Hz, 2H, Ar*H*), 3.79 (s, 3H, OCH_3), 3.41 (m, 1H, H-2), 2.62 (m, 2H, H-4), 1.75 (m, 2H, H-3), 1.27 (d, *J* = 6.4 Hz, 3H, 1-CH_3); **5**: colourless solid, mp 96–98 °C (acetone–hexane), $[\alpha]_D^{23}$ −0.50° (*c* 1, MeOH), ^{1}H NMR (300 MHz, $CDCl_3 + D_2O$) δ 7.10 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.83 (d, *J* = 8.7 Hz, 2H, Ar*H*), 3.79 (s, 3H, OCH_3), 2.83 (m, 1H, H-2), 2.55 (m, 2H, H-4), 1.55 (m, 2H, H-3), 1.10 (d, *J* = 6.6 Hz, 3H, 1-CH_3); EI–MS *m*/*z* 179 (M^+), 162, 147, 121, 44; **6**: colourless oil, $[\alpha]_D^{23}$ +0.06° (*c* 1, MeOH), IR (neat, cm^{-1}) 2900, 2155, 1610, 1580, 1510, 1460, 1242, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.4 Hz, 2H, Ar*H*), 3.79 (s, 3H, OCH_3), 3.40 (m, 1H, H-2), 2.90 (m, 2H, H-4), 2.30 (m, 2H, H-3), 1.80 (d, *J* = 6.9 Hz, 3H, 1-CH_3); EI-MS *m*/*z* 221 (M^+), 121; **7**: colourless oil, $[\alpha]_D^{23}$ −5.0° (*c* 1, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.4 Hz, 4H, Ar*H*), 6.82 (d, *J* = 8.4 Hz, 4H, Ar*H*), 3.78 (s, 6H, OCH_3), 2.8 (m, 4H, H-3), 2.65 (m, 4H, H-4), 1.74–2.0 (m, 2×H, H-3), 1.32 (d, *J* = 6.6 Hz, 2×3H, 1-CH_3), ES–MS *m*/*z* 408 ($M^+ + NH_4^+$).
13. *Insect bioassay:* Antifeedant and growth inhibitory assays were carried out with larvae of polyphagus pest insect *Spilarctia obliqua* (Noctuidae, Lepidoptera). The larvae were from a laboratory colony reared on artificial diet

under controlled conditions at 26 °C.[14] Antifeedant and growth inhibitory studies were conducted with pre-weighed broth instar larvae ($n = 30$ for each treatment) that were kept on a diet containing compounds and their derivatives under study. After 24 h, number of faecal produced were counted and % feeding-deterrency was analyzed.[15] The same experiment was continued for next 48 h. Weight of the insect larvae was taken daily. Weight gain or loss data was used to analyze % growth inhibition.[16] Azadirachtin from neem tree and diflubenzuron, which were used as a positive control, were obtained from SIGMA Chemicals Company, USA. Solvent acetone was used in negative control.

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