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# Synthesis of the C10–C17 fragment of aurisides and callipeltosides

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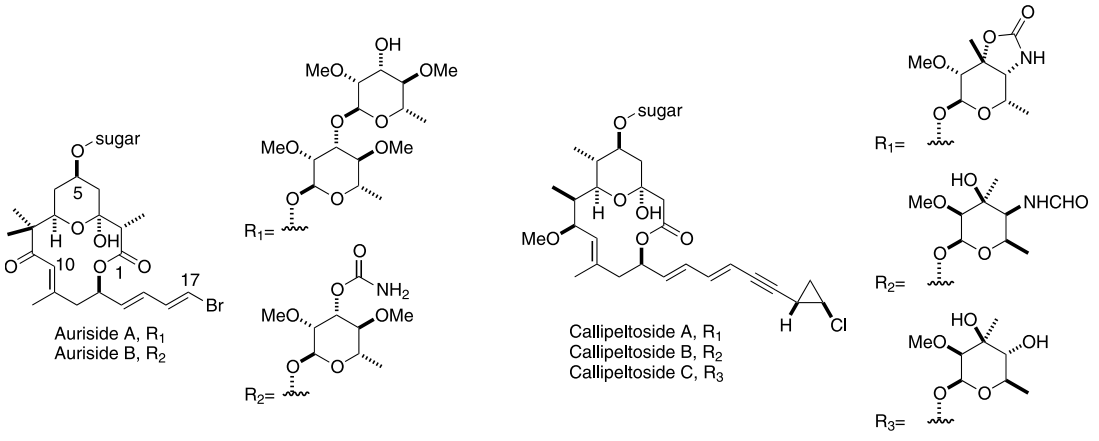
**Abstract**—The key unsaturated chiral C10–C17 fragment common on the synthesis of aurisides and callipeltosides was synthesized in six steps from 5-bromopentadienal via aldol condensation with Nagao's chiral auxiliary and further manipulation using Ohira's reagent and Negishi's carboalumination–iodination. © 2002 Elsevier Science Ltd. All rights reserved.

The cytotoxic halogenated and glycosylated macrolides aurisides A and B were isolated from the sea hare *Dolabella auricularia* by Yamada's group in 1996.[1] The macrolides callipeltosides A and B, which possess several structural similarities to the aurisides, were isolated from the marine sponge *Callipelta* sp. by Minale's group in the same year.[2] Both callipeltosides and aurisides contain rhamnose saccharides and disaccharides connected to their corresponding aglycone on the same carbon (C5). Auriside and callipeltoside aglycones contain a 14 membered macrolactone that includes a hemiketal ring, possess the same number of oxygens connected to the same carbons and are adorned with a pendant unsaturated chain bearing a halogen atom. Efforts toward the syntheses of these molecules have been reported.[3–6] The total synthesis of callipeltoside A has been accomplished by the Trost's and Evans' groups.[7,8]

In our synthetic approach, we designed a convergent strategy that could be utilized in the synthesis of both aurisides and callipeltosides.[5] Disconnection of the C9–C10 vinylic bond and the macrolactone in both molecules produces a common fragment valuable for both syntheses. In this letter, we report the synthesis of the key C10–C17 fragment.

The synthesis of fragment C10–C17 began from known bromoaldehyde **2**.[9] Aldol condensation using Evans oxazolidinone chiral auxiliary when the *N*-acyl group is an acetyl is known to give poor diastereoselectivity. Instead, Nagao's chiral *N*-acetyl thiazolidinethione

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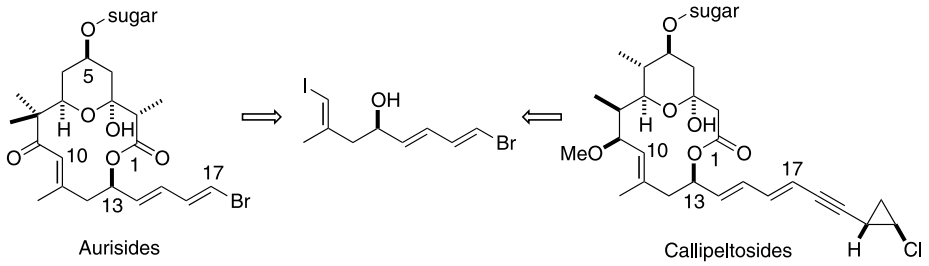


gives superior results when aldol condensations are carried out with unsaturated aldehydes.[10] Crimmins' group has shown that the stereochemistry of the newly formed chiral carbon in the aldol product using Nagao's chiral auxiliary is dependent on the nature and amount of the base used to generate the enolate, via chelated or non-chelated transition states.[11] Crimmins reported that the 'non-Evans' aldol product is obtained when 1 equiv. of base and one or more equivalents of Lewis acid are employed. Thus, when *N*-acetyl-4-(*S*)-isopropyl-thiazolidinethione **1** was reacted with dienal **2** in the presence of 1 equiv. of $TiCl_4$, and 1.2 equiv. of Hunigs' base, the (*R*)-aldol product **3** was obtained in 75% yield.[12]

Protection of the resulting (*R*)-alcohol **3** with triethylsilyltriflate occurred in excellent yield followed by reduction of Nagao's auxiliary to aldehyde **5** with Dibal-H. Homologation of aldehyde **5** to acetylene **7** was investigated using Ohira's reagent (**6**).[13] In order to avoid β-elimination, the reaction was carried out at −30°C and kept at that temperature for 6 h and then slowly warmed to room temperature and stirred for 20 h.

Negishi's carboalumination–iodination[14] did not occur with the silylether protected alcohol **7**, but only good yields were obtained when the reaction was carried out with the free alcohol **8**. The *E*-vinyliodide **9** was obtained stereospecifically in 65% yield.

In conclusion, vinyliodide **8** should be a useful intermediate for a convergent approach towards the synthesis of aurisides and callipeltosides. Chiral vinyl iodide **9** was prepared in six steps and 37% yield from bromodienal **2**. The C1–C9 northern fragments of aurisides and callipeltosides can be prepared from Grieco's bicyclic lactone, as reported previously.[5] The total syntheses of these macrolactones are underway in our laboratory.

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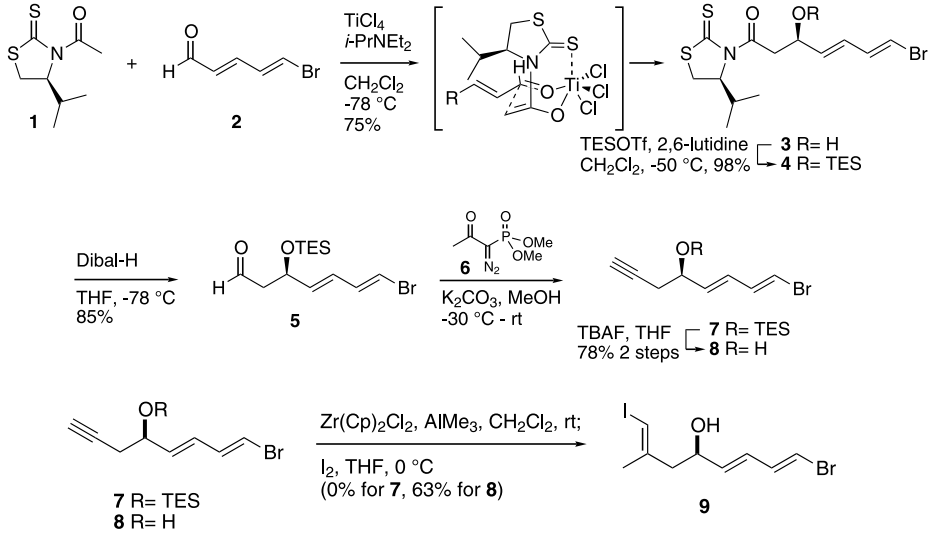

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12. Compound **3**: [α] +293 (*c* 1.0, $CHCl_3$); $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.72 (1H, dd, $J=13.3$, 11.0 Hz), 6.35 (1H, d, $J=13.3$ Hz), 6.26 (1H, ddd, $J=15.3$, 11.0, 1.2 Hz), 5.80 (1H, dd, $J=15.3$, 5.6 Hz), 5.17 (1H, t, $J=6.8$ Hz), 4.70 (1H, m), 3.69 (1H, dd, $J=17.8$, 3.1 Hz), 3.53 (1H, dd, $J=11.5$, 7.9 Hz), 3.29 (1H, dd, $J=17.6$, 8.6 Hz), 3.05 (d, $J=11.5$ Hz), 2.97 (1H, bs), 2.36 (1H, m), 1.07 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=6.8$ Hz); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 203.0 (C), 172.2 (C), 136.6 (CH), 134.6 (CH), 127.8 (CH), 109.5 (CH), 71.3 (CH), 67.9 (CH), 45.0 ($CH_2$), 31.0 ($CH_2$), 30.7 (CH), 19.0 ($CH_3$), 17.8 ($CH_3$).
Compound **4**: [α] +211 (*c* 1.0, $CHCl_3$); $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.69 (1H, dd, $J=13.6$, 10.9 Hz), 6.31 (1H, d, $J=13.6$ Hz), 6.16 (1H, dd, $J=15.2$, 10.9 Hz), 5.80 (1H, dd, $J=15.2$, 6.3 Hz), 5.05 (1H, t, $J=6.9$ Hz), 4.77 (1H, m), 3.61 (1H, dd, $J=16.6$, 7.8 Hz), 3.47 (1H, dd, $J=11.4$, 7.8 Hz), 3.26 (1H, dd, $J=16.6$, 4.7 Hz), 3.03 (1H, dd, $J=11.4$, 1.1 Hz), 2.37 (1H, m), 1.06 (3H, d, $J=6.7$ Hz), 0.97 (3H, d, $J=7.1$ Hz), 0.93 (9H, t, $J=8.0$ Hz), 0.59 (6H, q, $J=8.0$ Hz); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 203.0 (C), 171.0 (C), 136.9 (2CH), 127.4 (CH), 109.2 (CH), 71.8 (CH), 69.6 (CH), 46.4 ($CH_2$), 31.0 (CH), 30.9 ($CH_2$), 19.3 ($CH_3$), 18.0 ($CH_3$), 7.0 ($3CH_3$), 5.0 ($3CH_2$).
Compound **5**: $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 9.77 (1H, t, $J=2.1$ Hz), 6.71 (1H, dd, $J=13.6$, 10.8 Hz), 6.35 (1H, d, $J=13.6$ Hz), 6.19 (1H, dd, $J=15.1$, 10.8 Hz), 5.78 (1H, dd, $J=15.1$, 6.0 Hz), 4.70 (1H, ddd, $J=6.7$, 6.0, 5.3 Hz), 2.66 (1H, ddd, $J=16.1$, 6.7, 2.4 Hz), 2.56 (1H, ddd, $J=16.1$, 5.3, 2.0 Hz), 0.95 (9H, t, $J=7.9$ Hz), 0.61 (6H, q, $J=7.9$ Hz); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 201.1 (C), 136.6 (CH), 136.2 (CH), 127.6 (CH), 109.6 (CH), 68.3 (CH), 51.6 ($CH_2$), 6.9 ($3CH_3$), 5.0 ($3CH_2$).
Compound **7**: $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.74 (1H, dd, $J=13.5$, 10.9 Hz), 6.34 (1H, d, $J=13.5$ Hz), 6.20 (1H, dd, $J=15.2$, 10.9 Hz), 5.85 (1H, dd, $J=15.2$, 5.8 Hz), 4.31 (1H, ddd, $J=7.3$, 5.8, 5.7 Hz), 2.46 (1H, ddd, $J=16.5$, 5.7, 2.6 Hz), 2.36 (1H, ddd, $J=16.5$, 7.3, 2.6 Hz), 2.02 (1H, t, $J=2.6$ Hz), 0.97 (9H, t, $J=7.8$ Hz), 0.63 (6H, q, $J=7.8$ Hz); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 136.9 (CH), 136.3 (CH), 127.6 (CH), 109.1 (CH), 80.9 (C), 71.2 (CH), 70.5 (CH), 28.6 ($CH_2$), 6.9 ($3CH_3$), 5.0 ($3CH_2$).
Compound **8**: [α] −4.2 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.72 (1H, dd, $J=13.6$, 10.7 Hz), 6.37 (1H, dd, $J=13.6$, 0.5 Hz), 6.25 (1H, dddd, $J=15.4$, 10.8, 1.4, 0.5 Hz), 5.81 (1H, dd, $J=15.4$, 5.9, 0.8 Hz), 4.33 (1H, m), 2.51 (1H, ddd, $J=16.6$, 5.6, 2.7 Hz), 2.44 (1H, ddd, $J=16.7$, 6.6, 2.6 Hz), 2.16 (1H, bs), 2.08 (1H, t, $J=2.7$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 136.6 (CH), 134.8 (CH), 128.7 (CH), 110.0 (CH), 80.0 (C), 71.4 (CH), 70.0 (CH), 27.6 ($CH_2$).
Compound **9**: [α] +16.2 (*c* 1.0, $CHCl_3$); IR 3387, 3061, 3007, 2911, 1646, 1430, 1377, 1274 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.70 (1H, dd, $J=13.6$, 10.9 Hz), 6.34 (1H, d, $J=13.6$ Hz), 6.19 (1H, ddd, $J=15.3$, 11.0, 0.4 Hz), 6.04 (1H, s), 5.71 (1H, ddd, $J=15.3$, 5.9, 0.4 Hz), 4.28 (1H, q, $J=6.4$ Hz), 2.42 (2H, d, $J=6.4$ Hz), 1.88 (3H, s), 1.77 (1H, bs); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 144.1 (C), 136.7 (CH), 135.8 (CH), 127.9 (CH), 109.7 (CH), 78.4 (CH), 69.5 (CH), 47.3 ($CH_2$), 24.3 ($CH_3$).
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