Short and Convergent Synthesis of Asterriquinone Bl and Demethylasterriquinone Bl

Sir:

Asterriquinone Bl (1) and its de-O-methyl analog, demethylasterriquinone Bl (2), which are members of a group of bis-indolyl benzoxquinones, were isolated from strains of Aspergillus terreus and Pseudomassaria sp., respectively. Especially, the latter product 2 has been reported by Merck group to be the novel insulin receptor activator, that mimics the function of insulin, and therefore, is of potential therapeutic interest for the treatment of diabetes.

The total synthesis of the natural products 1 and 2 has been accomplished by Merck group using elegant strategies with the rearrangement of pyrandione.3) We describe herein a short and convergent synthesis of asterriquinone Bl (1) and demethylasterriquinone Bl (2).

The construction of 1 and 2 entailed the synthesis of three building blocks, the substituted indols 3 and 5 and the dibromoquinone 4, as depicted in Fig. 1.

Compounds 3 and 4 were prepared from 2-iodoaniline (6) and 2,5-dimethoxy-1,4-quinone (7) by the reported processes as shown in Scheme 1.4,5) The C2 substituted indol 5 was synthesized by chlorination of indol (8) with NCS to give 3-chloroindol (9), followed by treatment of prenyl-9-BBN.6)

Reaction of 4 with the lithiated 5 gave selectively the mono-substituted 10 without substitution of the bromide in 61% yield. This reaction seemed to proceed apparently in the Michael-retro Michael type based on the stability of the produced anion between the carbonyl and bromo groups.

Another indol moiety was further introduced onto 10 by using the lithiated 3 to afford the disubstituted 11 in 72%.

The synthesis was completed as follows. A solution of 11 in a mixture of dioxane and aq KOH solution was refluxed for 2 hours. After neutralization with Dowex 50WX8 (H type) and filtration, the filtrates were evaporated to the residue, which was chromatographed on silica gel [silica gel 60 (acidic), Kanto Chemicals] with PhMe-EtOAc (20:1) to give purple solids of 2 and 12 in 30% and 18% yields, respectively [on TLC (PhMe-EtOAc-AcOH=25:5:1), 2: Rf 0.23; 12: Rf 0.56]. Recrystallization of 2 from EtOAc-hexane gave purple needles: mp. 204°C (change of color at about 92°C). The synthetic product 2 was identical in all respects with natural demethylasterriquinone Bl.2,3)

The structure of the mono-bromide 12, which was isolated as a single isomer, was determined mainly by NMR studies as shown in Scheme 1. Alternatively, 2 was obtained from asterriquinone Bl (1) by de-O-methylation with aq KOH in EtOH in 78% yield.7) Asterriquinone Bl (1) was synthesized in 74% yield from 11 by treatment with NaOH in MeOH for 4 hours. Recrystallization from benzene gave purple prisms of 1: mp 211~213°C (change of color at about 112°C), which was

Fig. 1.

1: Asterriquinone Bl: R=Me
2: Demethylasterriquinone Bl: R=H
Scheme 1.

Conditions: (a) (Boc)$_2$O, i-Pr$_2$NEt/THF, 80°C, 5 days; 86% (b) (Trimethylsilyl)acetylene, Pd(PPh$_3$)$_2$Cl$_2$, CuI/Et$_3$N, rt, 40 minutes; 88% (c) t-BuLi/Et$_2$O, -20°C, then 4-bromo-2-methyl-2-buten, -78°C to rt, 5 hours; 86% (d) NaOEt/EtOH, reflux, 7.5 hours; 76% (e) Br$_2$ on Al$_2$O$_3$, sonicator, rt, 2 days; 51% (f) NCS/CCI$_4$, 0°C, 1 hour; 82% (g) Prenyl-9-BBN, Et$_3$N/THF, rt, 12 hours; 72% (h) LiN(TMS)$_2$/THF, -78°C to rt, 3 hours; 61% (i) s-BuLi/THF, -78°C to rt, 2 hours; 72% (j) aq. KOH/dioxane, reflux, 2 hours; 30% of 2 (k) NaOH/MeOH, rt, 4 hours; 74% (l) aq. KOH/EtOH, reflux, 2 hours; 78%
Table 1. Physico-chemical properties of compounds.

<table>
<thead>
<tr>
<th>Compds.</th>
<th>Mp (°C)</th>
<th>$^1$H-NMR (400, 500 or 600MHz; δ ppm; J Hz)</th>
<th>$^{13}$C-NMR(125MHz; δ ppm)</th>
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<tr>
<td>1 211-213 (prisms from benzene)</td>
<td>211-213</td>
<td>$^1$H-NMR(CDCl$_3$): δ 1.48(6H, s), 1.79(3H, s), 1.83(3H, s), 3.60(2H, d, J=7.0Hz), 3.68(3H, s), 3.79(3H, s), 5.13(1H, dd, J=10.6&amp;1.0Hz), 5.18(1H, d, J=17.4&amp;1.0Hz), 5.40-5.47(1H, m), 6.09(1H, dd, J=17.4&amp;10.6Hz), 7.02-7.16(4H, m), 7.26(1H, d, J=8.0Hz), 7.31(1H, d, J=8.0Hz), 7.40(1H, d, J=8.0Hz), 7.56(1H, d, J=2.8Hz), 8.12(1H, br s), 8.52(1H, br s)</td>
<td>$^{13}$C-NMR(CDCl$_3$): δ 18.0, 25.7, 26.8, 27.1, 30.8, 39.3, 60.0, 60.7, 77.2, 101.7, 105.8, 110.6, 112.3, 118.7, 119.3, 120.2, 120.6, 120.7, 121.9, 122.0, 122.2, 124.1, 126.7, 127.4, 129.8, 133.6, 134.5, 135.0, 142.1, 145.4, 154.4, 156.3, 183.5, 184.0</td>
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<tr>
<td>2 203-204 (needles from EtOAc-hexane)</td>
<td>203-204</td>
<td>$^1$H-NMR((CD$_3$)$_2$CO): δ 1.52(6H, s), 1.75(3H, s), 1.77(3H, s), 3.64(2H, d, J=7.0Hz), 5.00(1H, dd, J=10.4&amp;1.0Hz), 5.09(1H, dd, J=17.0&amp;1.0Hz), 5.44-5.51(1H, m), 6.16(1H, dd, J=17.0&amp;10.4Hz), 6.91-7.06(4H, m), 7.28(1H, d, J=7.8Hz), 7.32(1H, d, J=7.8Hz), 7.44(1H, dd, J=7.0&amp;1.0Hz), 7.62(1H, d, J=3.0Hz), 9.40(1H, br s), 10.07(1H, br s), 10.43(1H, br s)</td>
<td>$^{13}$C-NMR(CDCl$_3$): δ 18.0, 25.7, 26.9, 30.8, 39.3, 99.5, 104.7, 110.7, 111.0, 111.7, 112.3, 118.6, 119.8, 120.0, 120.5, 122.1, 122.2, 124.2, 126.0, 126.7, 128.2, 128.5, 129.0, 133.6, 134.7, 135.2, 142.5, 145.5</td>
</tr>
<tr>
<td>10 58-60 (prisms from benzene)</td>
<td>58-60</td>
<td>$^1$H-NMR((CD$_3$)$_2$CO): δ 1.45(6H, s), 4.23(3H, s), 5.02(1H, dd, J=11.0&amp;1.0Hz), 5.04(1H, dd, J=18.0&amp;1.0Hz), 6.05(1H, dd, J=18.0&amp;11.0Hz), 6.94(1H, dd, J=8.0&amp;8.0Hz), 7.06(1H, dd, J=8.0&amp;8.0Hz), 7.19(1H, d, J=8.0Hz), 7.34(1H, d, J=8.0Hz), 10.36(1H, br s)</td>
<td>$^{13}$C-NMR(CDCl$_3$): δ 26.8, 27.7, 39.3, 62.0, 105.5, 110.9, 113.2, 118.7, 119.4, 120.3, 122.4, 126.5, 134.8, 134.8, 142.3, 145.1, 145.5, 156.5, 174.5, 177.7</td>
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<tr>
<td>11 213-215 (needles from EtOAc-hexane)</td>
<td>213-215</td>
<td>$^1$H-NMR((CD$_3$)$_2$CO): δ 1.48(6H, s), 1.73(3H, s), 1.75(3H, s), 3.64(2H, d, J=7.0Hz), 5.06(1H, dd, J=11.0&amp;1.0Hz), 5.09(1H, dd, J=18.0&amp;10.0Hz), 5.42-5.47(1H, m), 6.09(1H, dd, J=18.0&amp;11.0Hz), 6.91-7.07(5H, m), 7.27(1H, d, J=8.0Hz), 7.34(1H, d, J=8.0Hz), 7.67(1H, d, J=3.0Hz), 10.37(1H, br s), 10.80(1H, br s)</td>
<td>$^{13}$C-NMR(CDCl$_3$): δ 18.0, 25.7, 26.8, 27.7, 30.7, 39.3, 106.0, 109.4, 110.9, 113.2, 118.8, 119.8, 120.3, 121.0, 122.0, 122.3, 122.5, 124.7, 125.0, 126.6, 128.6, 133.2, 133.9, 134.8, 135.0, 137.3, 141.9, 142.0, 145.2, 145.7, 177.7</td>
</tr>
<tr>
<td>12 107-110 (needles from EtOAc-hexane)</td>
<td>107-110</td>
<td>$^1$H-NMR(CD$_3$CO): δ 1.52(6H, s), 1.76(3H, s), 1.78(3H, s), 3.65(2H, d, J=7.0Hz), 5.01(1H, d, J=10.4Hz), 5.11(1H, d, J=17.0Hz), 5.42-5.53(1H, m), 6.17(1H, dd, J=17.0&amp;10.4Hz), 6.90-7.08(4H, m), 7.28(1H, d, J=7.8Hz), 7.33(1H, d, J=7.8Hz), 7.45(1H, br d, J=7.0Hz), 7.62(1H, d, J=3.0Hz), 10.10(1H, br s), 10.46(1H, br s)</td>
<td>$^{13}$C-NMR(CDCl$_3$): δ 18.0, 25.7, 26.8, 27.6, 30.7, 39.3, 104.7 105.8, 110.9, 113.0, 115.7, 118.6, 119.9, 120.3, 120.6, 122.2, 122.3, 124.4, 124.2, 125.9, 126.7, 128.0, 133.6, 134.9, 135.1, 141.2, 141.8, 141.9, 145.2, 149.0, 179.4, 180.9</td>
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identical in all respects with the natural product.\textsuperscript{1,3}

At the heart of the synthesis described herein is the selective introduction of two different components 3 and 5 onto the benzoquinone core 4.

Acknowledgment

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References


