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First Total Synthesis of Cleroindicin B, (±) Cleroindicin C and E

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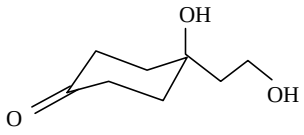
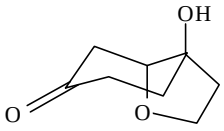
Abstract: Cleroindicin B, C and E, three new natural products originally isolated from *Clerodendrum indicum*, have been synthesized (in racemic forms for Cleroindicin C and E) by a facile route, starting from 2-(*p*-methoxy-phenyl) ethanol **1**. The (±) cleroindicin C (**5**) has been resovled by the enantioselective inclusion methodology.

Keywords: Cleroindicin B, cleroindicin C, cleroindicin E, enantioselective inclusion methodology.

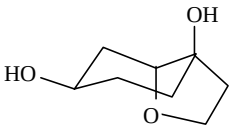
The isolation of cleroindicins B, C and cleroindicin E, together with three novel related compounds cleroindicins A, D and F, from chinese folk medicine *Clerodendrum indicum* Linn. was reported before[1]. Pharmaceutical studies showed that cleroindicin C has certain anticancer activity, so its total synthesis attracted our considerable interest.



Cleroindicin B



Cleroindicin C



Cleroindicin E

The commercially available 2-(*p*-methoxyphenyl) ethanol **1** was selected as the starting material. Compound **1** was treated under the Birch reduction condition[2] for 5 h and 1 mol/L HCl was added to adjust the pH to 3. When the reaction mixture was stirred at -5°C for 12 h, the 2-(cyclohex-1-en-4-one) ethanol **3** was acquired as a colorless oil in 92% yield. But hydrolysis at ambient temperature for 12 h gave cleroindicin B in 68% yield[3]. In order to build a *cis* cyclohexane-tetrahydrofuran ring, the normal oxidative cyclization of **3** was selected due to its simplicity and efficiency[4]. Compound **3** was oxidized with *m*-chloroperoxybenzoic acid[5] producing the (±) cleroindicin C **5** in 67% yield directly. It should be noted that the epoxide intermediate **4** could not be isolated from the reaction mixture under such conditions, which was directly converted into compound **5** under the catalysis of *m*-chlorobenzoic acid originating from *m*-chloroperoxybenzoic acid. The (±) cleroindicin E (**6**) was acquired from **5** by reduction with $NaBH_4$, because the hydroxyl group locates in the equatorial

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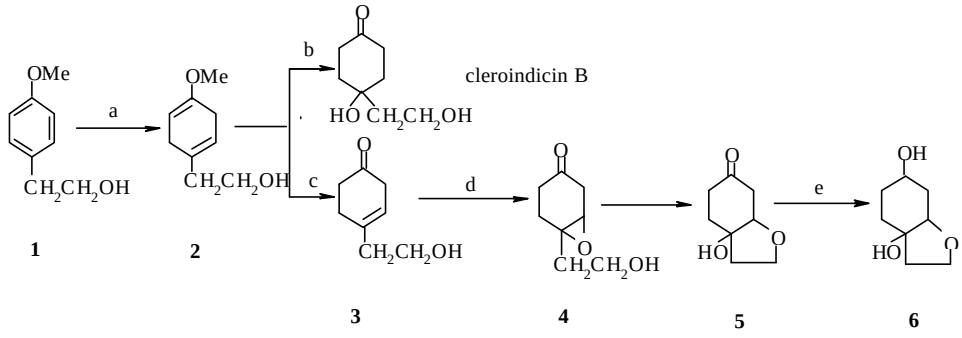
form[6]. The NMR spectra and TLC behavior of **5** and **6** were consistent with those of natural cleroindicins C and E[7].

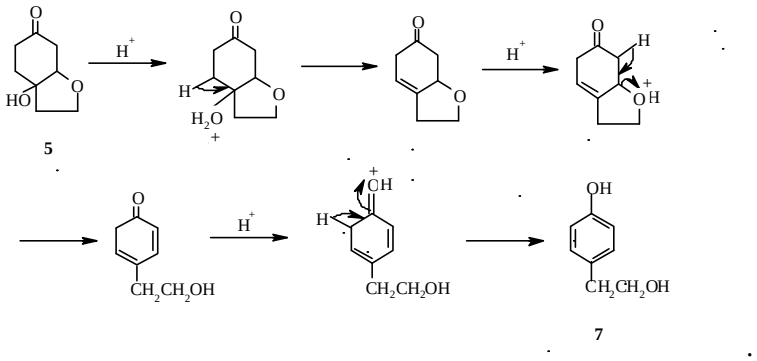
Scheme 1



Reagents and conditions: (a) ⅰ. NH_3(liquid), Li, *t*-BuOH, THF, -40°C, 4 h; ⅱ. NH_4Cl, -40°C, 1 h; (b) 1mol/L HCl, pH=3, rt, 12 h, 68% from **1**; (c) 1 mol/L HCl, pH=3, -5°C, 12 h, 92% from **1**; (d) mCPBA, CH_2Cl_2, 0°C, 6 h; (e) $NaBH_4$, CH_3OH, 0°C, 8 h, 82% from **5**.

Interestingly, we found that compound **5** was unstable in the presence of trace acid. After storage in the refrigerator for a few weeks, it turned into 2-(*p*-hydroxyl phenyl)ethanol **7**. This phenomenon could be interpreted by the mechanism suggested in **Scheme 2**. The acid catalyst (*m*-chlorobenzoic acid) was derived from the epoxydation process. The structures of the compounds **3** and **7** were characterized by NMR spectra[8].

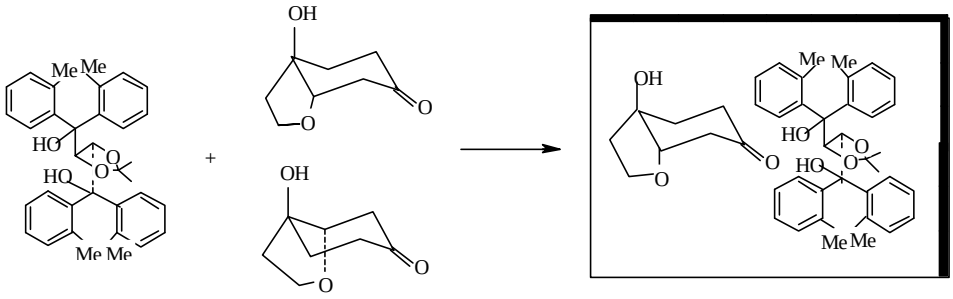
Scheme 2



When a suspension of finely powdered (R, R)-(-)-trans-2, 3-bis (hydroxydiphenylmethyl)-1, 4-dioxaspiro [5.4] decane **8** and the racemate **5** (the molar ratio=1:2) in water containing hexadecyltrimethylammonium bromide as a surfactant was stirred at room temperature for 8 h[9], an inclusion complex of **8** and (–)-**5** (cleroindicin C) was formed as fine crystals, which was column chromatographed with cyclohexane containing increasing amounts of EtOAc, to give (–)-**5** in 82% ee {47% yield, $[\alpha]_D^{20}$

–18.3 (*c* 0.37, MeOH)}. The optical purity of (–)-**5** was determined by comparison of the $[\alpha]_D^{20}$ value of cleroindicin C with that reported[1].

Scheme 3



8 **5**

Acknowledgment

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References and notes

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3. **Cleroindicin B:** colorless oil, ^{1}H-NMR (400MHz. C_5D_5N): *d* 1.84 (dt, 2H, J=13.2, 4.6Hz, Ha-2, 6), 2.05 (t, 2H, J=6.6Hz, H-7), 2.16 (dt, 2H, J=13.2, 4.8Hz, He-2, 6), 2.32 (dt, 2H, J=13.6, 4.2Hz, He-3, 5), 2.95 (dt, 2H, J=13.6, 6.2Hz, Ha-3, 5), 4.18 (t, 2H, J=6.6Hz, H-8); ^{13}C-NMR (100MHz): *d* 37.6 (2C, C-2, 6), 37.8 (2C, C-3, 5), 44.4 (C-7), 58.8 (C-8), 69.8 (C-1), 211.5 (C-4). The above data were consistent with the literature 1.
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7. **Cleroindicin C:** colorless oil, ^{1}H-NMR (400MHz. C_5D_5N): *d* 2.02 (m, 1H, H-3), 2.07 (m, 1H, H-3), 2.13 (m, 1H, H-5), 2.22 (m, 1H, H-5), 2.32 (ddd, 1H, J=15.8, 10.8, 3.6, Ha-6), 2.63 (ddd, 1H, J=11.6, 6.2, 3.4, He-6), 2.76 (dd, 1H, J=15.7, 4.2, H-8), 2.97 (dd, 1H, J=15.7, 4.2, H-8), 3.91 (m, 2H, H-2), 4.25 (t, 1H, J=4.2, H-9); ^{13}C-NMR (100MHz): *d* 34.3 (C-5), 35.8 (C-6), 40.9 (C-3), 43.1 (C- 8), 66.3 (C-2), 76.9 (C-4), 84.6 (C-9), 209.9 (C-7).
   Cleroindicin E: colorless oil, ^{1}H-NMR (400MHz. C_5D_5N): *d* 1.93 (m, 1H, H-5), 2.12 (m, 1H, H-5), 2.03 (m, 1H, H-6), 2.18 (m, 1H, H-6), 2.15 (m, 2H, H-3), 2.24 (m, 1H, H-8), 2.48 (m,

1H, H-8), 3.94 (t, 1H, J=8.4, He-2), 4.05 (m, 1H, Ha-2), 4.24 (t, 1H, J=4.0, H- 9), 4.34 (tt, 1H , J=10.8, 4.2, H-7); ^{13}C-NMR (100MHz): δ 31.8 (C-6), 33.2 (C-5), 36.8 (C-8), 39.8 (C-3), 65.4 (C-2), 66.0 (C-7), 75.3 (C-4), 82.3 (C-9). The above data were consistent with the literature 1.

8. *Selected data.* For **3**: colorless oil, ^{1}H NMR (C_5D_5N) δ 2.85 (d, 2H, *J*=1.7 Hz, H-2), 5.51 (t, 1H, *J*=1.7 Hz, H-3), 2.46 (t, 2H, *J*=6.6 Hz, H-7), 3.94 (t, 2H, *J*=6.6 Hz, H-8), 2.38 (t, 2H, *J*=6.7 Hz, H-5), 2.42 (t, 2H, *J*=6.7 Hz, H-6); ^{13}C NMR (C_5D_5N) δ 29.3 (C-5), 37.7 (C-2), 39.0 (C-6), 41.1 (C-7), 60.5 (C-8), 119.6 (C-3), 136.6 (C-4), 209.4 (C-1).
For **7**: colorless crystal, ^{1}H NMR (C_5D_5N) δ 3.00 (t, 2H, *J*=6.8 Hz, H-7), 4.05 (t, 2H, *J*=6.8 Hz, H-8), 7.16 (d, 2H, *J*=8.4 Hz, H-2, H-6), 7.25 (d, 2H, *J*=8.4 Hz, H-3, H-5); ^{13}C NMR (C_5D_5N) δ 39.4 (C-7), 63.8 (C-8), 115.9 (C-4), 130.4 (C-2, C-6), 130.5 (C-3, C-5), 157.05 (C-1).
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