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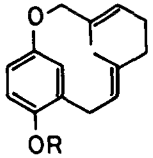
SYNTHESIS OF ARNEBINOL, AN INHIBITOR OF PROSTAGLANDIN BIOSYNTHESIS

Kenji Mori*, Masayuki Sakakibara and Michiru Waku
Department of Agricultural Chemistry, The University of Tokyo
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

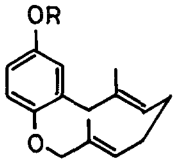
Abstract: A new ansa-type compound, arnebinol **1**, was synthesized.

Arnebinol **1**, isolated from Arnebia euchroma (Boraginaceae) as an inhibitor of prostaglandin biosynthesis,1) has an ansa-type monoterpenylbenzenoid structure. We report here a synthesis of this compound **1**, accompanied with its regioisomer **2**. A key step of our synthesis involved the reductive allylation of benzoquinone2) with an allyltin compound **3**, prepared from geranyl acetate in 6 steps.

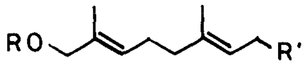
Geranyl acetate was converted into **4** as reported previously.3) Silylation($\underline{t}$-BuMe$_2$SiCl, TEA, DMAP, CH$_2$Cl$_2$)4) of **4** gave an acetoxy silyl ether **5** (94.2% yield), which was hydrolized(K$_2$CO$_3$, aq. MeOH)5) to give a diol monosilyl ether **6** (97.7% yield). Chlorination(MsCl, LiCl, $\underline{s}$-collidine, DMF)6) of **6** gave a chloride **7** (95.9% yield), which was stannylated($\underline{n}$-Bu$_3$SnLi)7) to give the allyltin compound **3** (74.4% yield). The reductive allylation of benzoquinone2) with **3** in the presence of BF$_3$·Et$_2$O gave a hydroquinone derivative **8** (91.0% yield). Acetylation(Ac$_2$O, DMAP, Py)8) gave a silylated diacetate **9** (79.8% yield), which was desilylated(AcOH-H$_2$O-THF, 3:1:1)9) to give an allylic alcohol **10** (61.0% yield). Chlorination of **10** with Ph$_3$P/CCl$_4$10)(34.2% yield) or NCS-Me$_2$S/CH$_2$Cl$_2$11)(71.6% yield) gave an allylic chloride **11**. Intramolecular cyclization of **11**



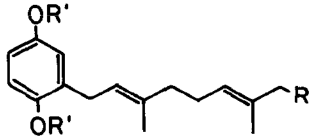
1 R = H
12 R = Ac



2 R = H
13 R = Ac



4 R = H R' = OAc
5 R = SiMe$_2$Bu^t R' = OAc
6 R = SiMe$_2$Bu^t R' = OH
7 R = SiMe$_2$Bu^t R' = Cl
3 R = SiMe$_2$Bu^t R' = SnBu$^n_3$



8 R = OSiMe$_2$Bu^t R' = H
9 R = OSiMe$_2$Bu^t R' = Ac
10 R = OH R' = Ac
11 R = Cl R' = Ac

with K_2CO_3-NaBr in acetone, freshly distilled after drying over anhyd. $CaCl_2$, under a high dilution condition(845 μg/ml, 56°C, 68 hr) gave a regioisomeric mixture of the cyclized products, **12** and **13**, (76.9% yield), which was hydrolized[5] to give arnebinol **1**[12](20.8% yield) and its regioisomer named isoarnebinol **2**[13](32.1% yield), after the HPTLC separation.[14] The ^{1}H-NMR spectrum(400 MHz) of the synthetic **1** was identical with that of the natural **1**.

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12) Colorless crystals from benzene, mp 159-160°C(lit.[1] mp 163.5-164°C); IR(KBr, cm^{-1}) 3430, 3050, 2930, 1603, 1505, 1455, 1440, 1420, 1340, 1270, 1250, 1190, 1141, 1085, 985, 975, 935, 908, 892, 860, 848, 832, 802, 793, 695, 637, 575, 540, 470; UV(nm, log ε) 203(4.36), 221sh, 291.5(3.48); ^{1}H-NMR($CDCl_3$, δ) 1.24(s, 3H), 1.50(s, 3H), 2.14(br s, 1H), 2.34(t, J=7 Hz, 2H), 2.49(br s, 1H), 3.07(br s, 1H), 3.30(br s, 1H), 4.35(s, 1H), 4.52(br s, 2H), 5.51 (t, J=7 Hz, 1H), 5.67(t, J=7 Hz, 1H), 6.55(dd, J=3 & 8.5 Hz, 1H), 6.59(d, J=8.5 Hz, 1H), 7.44(d, J=3 Hz, 1H); MS(m/z) 244.1463 (244.1464 for $C_{16}H_{20}O_2$).
13) Rhombohedral crystals from benzene-*n*-hexane, mp 163-165°C; IR(KBr, cm^{-1}) 3405, 3040, 2930, 1586, 1497, 1460, 1435, 1385, 1327, 1267, 1232, 1193, 1165, 1147, 1100, 1075, 1030, 960, 940, 921, 909, 880, 858, 830, 815, 802, 773, 760, 630, 603, 560, 502; UV(nm, log ε) 203.5(4.49), 231sh, 290(3.54); ^{1}H-NMR($CDCl_3$, δ) 1.57(s, 3H), 1.59(s, 3H), 2.15(m, 4H), 3.19(d, J=6 Hz, 2H), 4.39(s, 2H), 4.47(s, 1H), 4.83(t, J=6 Hz, 1H), 5.08(t, J=8 Hz, 1H), 6.60(d, J=3 Hz, 1H), 6.64(dd, J=3 & 8 Hz, 1H), 6.85(d, J=8 Hz, 1H); MS(m/z) 244.1438(244.1464 for $C_{16}H_{20}O_2$).
14) Silica gel 60F_{254} pre-coated for nano-TLC(Merck Art. 5628); triply developed with $CHCl_3$.

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