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THE DESIGN, SYNTHESIS AND EVALUATION OF A,C,D-RING ANALOGS OF THE FUNGAL METABOLITE K-76 AS COMPLEMENT INHIBITORS: A POTENTIAL PROBE FOR THE ABSOLUTE STEREOCHEMISTRY AT POSITION 2

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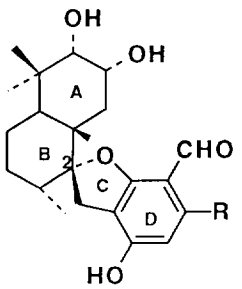
Abstract: In an attempt to synthesize stereochemically pure new A, C, D-ring analogs of the natural product complement inhibitor K-76, compounds (**20-24**) were prepared and the representative one (**23**) was evaluated for its ability to inhibit complement-mediated erythrocyte lysis in both the classical and alternative pathways. Compounds synthesized as part of this study suggest that the terpenoid diol component of K-76 may not be essential for complement inhibition.

In continuation of our ongoing program[1] for the design, synthesis and evaluation of new A,C,D-ring analogs of K-76 (**1**)[2] as potential complement inhibitors, we observed a lack of stereoselectivity during the cyclization step aimed towards the synthesis of the desired prototypes **4** reported earlier.[1] The mechanism of the



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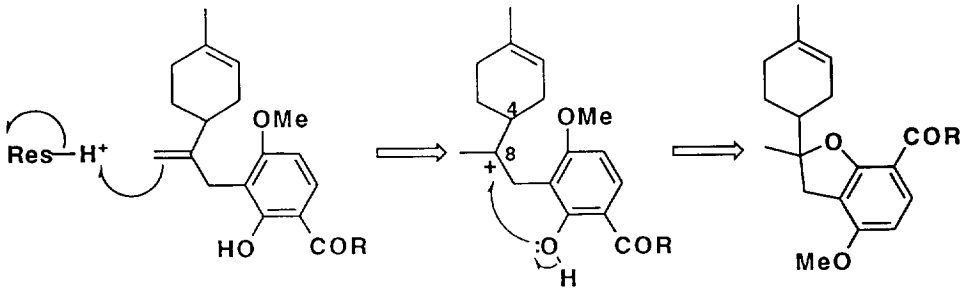
K-76 : R = CHO
K-76COONa : R = COONa

cyclization is proposed as the protonation of the double bond and the formation of the more stable carbonium ion (**3**) on C-8 (limonene numbering), followed by the nucleophilic attack by the phenolic hydroxyl, with the resulting loss of a proton in order to form the cyclized product **4** (Scheme 1). The proposed mechanism suggested

Scheme 1

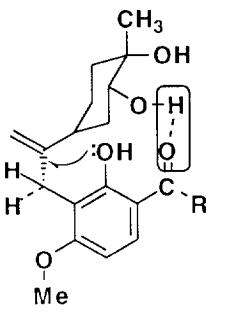


2 3 4

R = OH
R = OEt
R = H

that the steric hinderence provided by the C-4 chiral center alpha to the carbonium ion, is not sufficient to induce asymmetry in C-8 of the cyclized product. In order to overcome this problem, the steric and electronic factors that contribute to the cyclization, were studied. After analysis of the Drieding model of the starting material **2**, it was concluded that if interactions could be provided between the aromatic carbonyl group and the cyclohexene ring, a preferred conformation of the starting material would allow asymmetric attack of C-8 by the phenolic hydroxyl. In order to provide these interactions, it was decided to explore the functionality of the endocyclic double bond of the alicyclic moiety. In fact, the regio- and stereospecific hydroxylation of Δ1,2 may provide not only the proper hydrogen bonding interactions to induce the cyclization, but also generate the native idol functionalization of C-1

Figure 1



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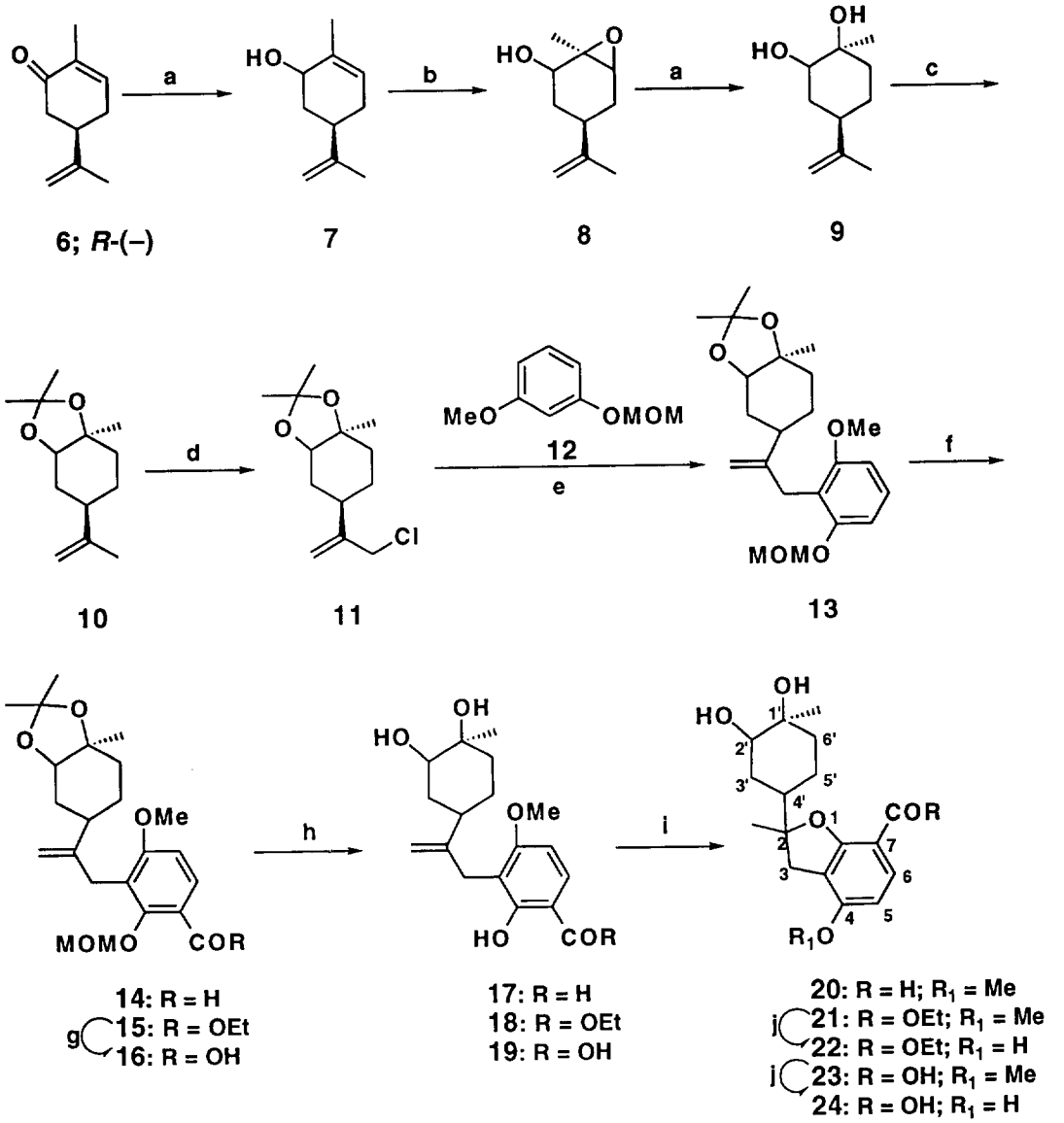
and C-2. The interaction of either alcoholic hydroxyl in the alicyclic moiety with the carbonyl oxygen of the molecule **5** would place the phenolic hydroxyl in such a position that only one diastereomer would be possible (Figure 1). Based on this hypothesis, we report the synthesis of the desired A, C, D-ring analogs (**20-24**) which may be treated as potential probes for the absolute stereochemistry at position 2 of K-76 and also evaluated as tools for finding the essential pharmacophore of this important natural product.

Scheme 2[a]



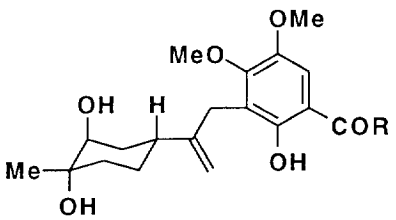
[a] Reagents: (a) $LiAlH_4$, THF; (b) *t*-BuOOH, $VO(AcAc)_2$; (c) $Me_2C(OMe)_2$, *p*-TsOH; (d) $Ca(ClO)_2$, CO_2, CCl_4; (e) *n*-BuLi, TMEDA, CuI; (f) *n*-BuLi, TMEDA, HCO_2Et (R = H), CO_3Et_2 (R = OEt); (g) 30% aq NaOH, EtOH; (h) SiO_2, 1% AcOH, EtOAc; (i) Amberlyst® 15, CH_2Cl_2; (j) *t*-BuSLi, HMPA.

The synthetic strategy is outlined in Scheme 2. The appropriate allylic chloride **11**, which will constitute the

the skeleton of ring A of K-76, was synthesized from *R*-(-)-carvone (**6**) in five steps. In fact, the carveol epoxide (**8**) was prepared from **6** by the method of Itoh et al.[3] Reduction[4] of **8** by $LiAlH_4$ followed by the ring closure of carvediol (**9**) with 2,2-dimethoxypropane gave the acetonide **10** which was then chloromethylated[5] by treating with 1.03 M aq calcium hypochlorite solution in presence of dry ice at 0 °C furnish the desired allylic chloride (**11**). On the other hand, the synthesis of 3-methoxymethoxyanisole (**12**) which will generate the D-ring, was prepared by the method reported earlier.[1] In a process analogous to that described in the same report,[1] the arylcuprate reagent derived from **12** was allowed to react with the allylic chloride (**11**). The desired key intermediate **13** was isolated as an oil[6] in 88% yield after column chromatography. The next step was the treatment of **13** with the TMEDA–*n*-BuLi complex in hexane, under the conditions developed by Christensen,[7] followed by the reaction with ethyl formate or diethyl carbonate at low temperature (–78 °C) which furnished the aldehyde **17** or the ester **15** in 46% and 53% yield respectively. Consequently, the acid **16** was easily obtained in 96% yield by the facile hydrolysis of **15** under alkaline condition. Compounds **14-16** were then deprotected by the silica gel and 1% acetic acid to generate alcoholic hydroxyls in the alicyclic moiety and the free phenolic hydroxyl group (**17-19**; 79-96% yields) which was required for the next cyclization step. After stirring **17-19** with Amberlyst® 15 resin in methylene chloride at room temperature,[8] the desired prototype compounds **20, 21** and **23** were obtained in 91-92% yields.[9] Ultimately, the compounds **21** and **23** were demethylated by treating with lithium *t*-butylthiolate as reported earlier[1] to yield the additional analogs **22** and **24**.

The ^1H- and ^{13}C-NMR spectra of these target compounds revealed duplication of the resonance signals indicating that both diastereomers were present in approximately equimolar quantities. Apparently the proposed hydrogen bond was not adequate to stabilize the 12-member ring intermediate (Figure 1) or if formed, the 12-member ring did not properly orient the substituents for asymmetric attack. Most likely, the lack of interactions between alicyclic and aromatic substituents resulted in an extended conformation of **5** (Figure 2) for which cyclization yielded a diastereomeric mixture.

Figure 2



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The representative compound **23** was assayed for its ability to inhibit complement-mediated erthrocyte lysis in both the classical[1,10] and alternative pathways.[11-12] The results are summarized as IH_{50} values in Table 1 which revealed lower inhibitory activity with respect to the natural product. Compound **19** was also examined for the capacity to inhibit classical pathway erythrocyte lysis and yielded 24% inhibition at 2000μM, the highest concentration tested. These results suggests that the terpenoid diol may not be necessary for complement inhibition. Compounds **17, 18,** and **20-22** were not assayed for complement inhibition due to their poor aqueous solubilities.

Table 1. The Inhibition of Human Complement by 7-Carboxy-4-methoxy-2-(*R*,*S*)-methyl-2-[1'*S*,2'*R*-dihydroxy-1'-methylcyclohex-4'*R*-yl]-(3H)-benzofuran (**23**); Concentration[a] (μM) Yielding 50% Inhibition.

Compound	Classical pathway IH_{50} (μM)	Alternate pathway IH_{50} (μM)
K-76COONa	570 (± 170; n=9)	850 (n=1)
23	1600 (± 28; n=2)	> 2550 (n=1)

[a] Values reported are the mean (± standard deviation; sample number, n)

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References and Notes

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6. Spectral data of **13**:
   $[\alpha]^{25}D$ = +12.98° (c 9.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, ppm) δ 1.35 (s, 3H), 1.43 (s, 3H), 1.48 (s, 3H), 1.25-2.30 (m, 7H), 3.39 (s, 2H), 3.43 (s, 3H), 3.78 (s, 3H), 3.94 (dd, 1H, *J*=6.3 and 7.5 Hz), 4.38 (s, 1H), 4.73 (s, 1H), 5.14 (s, 2H), 6.58 (d, 1H, *J*=8.4 Hz), 6.73 (d, 1H, *J*=8.4 Hz), 7.14 (t, 1H, *J*=8.4 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) δ 27.65, 27.99, 28.12, 29.14, 32.88, 34.44, 38.43, 55.82, 56.01, 79.59, 80.01, 94.39, 104.63, 107.02, 107.28, 107.71, 117.76, 127.19, 152.15, 156.03, 158.59; IR (Neat, cm^{-1}) ν_{max} 3030-2820 (br), 1640, 1595, 1470, 1380, 1255, 1205, 1155, 1100, 1070, 1020, 925, 890, 780, 740; Anal. calcd. for $C_{22}H_{32}O_5$: C, 70.21; H, 8.51. Found: C, 70.06; H, 8.56.
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9. Spectral data of the representative compound **23**:
White powder; mp 184-186 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 1.14 (s, 3H), 1.55 (s, 3H), 1.26-2.32 (m, 7H), 2.80 (bs, 2H), 3.00 (dd, 1H, *J*=7.5 and 7.5 Hz); 3.15 (dd, 1H, *J*=2.76 and 2.76 Hz), 3.52 (dd, 1H, *J*=5.7 and 10.4 Hz), 3.95 (s, 3H), 6.55 (d, 1H, *J*=8Hz), 7.86 (d, 1H, *J*= 8Hz); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) δ 21.59, 24.16, 27.07, 28.74, 31.29, 36.88, 45.89, 55.55, 70.74, 75.02, 91.96, 104.59, 104.71, 120.17, 130.33, 156.15, 160.33, 171.86; IR (KBr, cm^{-1}) ν_{max} 3340, 3000-2820(br), 1670, 1615, 1500, 1435, 1265, 1100, 1070, 1030, 900, 770; Anal. calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.36; H, 7.21.
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