($CDCl_3$) δ 7.67 (bs, 1H), 7.43-7.08 (m, 10H), 5.11 (s, 1H), 3.27 (d, *J*=20.1 Hz, 2H), 3.10 (d, *J*=5.1 Hz, 3H), 2.02 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −92.2 (t, *J*=19.8 Hz, 1F); MS, m/z (relative intensity) 341 (M^+, 2), 294 (23), 264 (100), 244 (83), 232 (21); IR (neat) 3000, 1600, 1560, 1470, 1530, 1330, 1250, 730, 680 cm^{-1}.

12. Spectroscopic data of **4a** is as follows. **4a**: mp 124-125 °C; ^1H NMR ($CDCl_3$) δ 7.41-7.17 (m, 10H), 6.67 (d, *J*= 1.1 Hz, 1H), 6.24 (d, *J*=1.0 Hz, 1H), 5.35 (s, 1H), 3.43 (s, 3H), 2.11 (s, 3H); MS, m/z (relative intensity) 321 (M^+, 18), 212 (100), 184 (75), 109 (47); IR (KBr) 3350, 1620, 1520, 1380, 1170, 750, 690 cm^{-1}.
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Enantioselective Synthesis of a *trans*-Hydrindane System for the Preparation of Vitamin D Metabolites§

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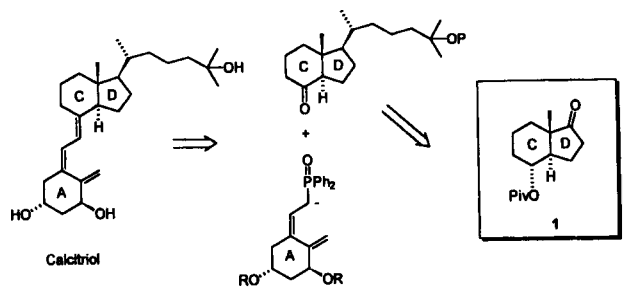
Received November 15, 1996

Vitamin D metabolites and their analogs are receiving an intense attention due to their medicinal and therapeutic importances.[1] *trans*-Hydrindane system constitutes the C/D ring synthon of these vitamin D compounds and continuous efforts have been made to develop new methods for constructing this structure. Approaches based on Lythgoe's methodology[2] *via* a convergent Wittig coupling of the A-ring fragments and this bicyclic C/D-ring system remain particularly attractive in the synthesis of various vitamin D related analogs. Hoffmann-LaRoche group's synthesis[3] of 1α, 25-dihydroxycholecalciferol (calcitriol), a medicinally active vitamin D_3 metabolite, is the classical example employing this strategy (Scheme 1).

Control of vicinal stereochemistry is very important in constructing this *trans* "angularly methylated" hydrindane and much effort has been directed to this area. For the enantioselective synthesis of angularly methylated hydrindanes, various routes have been devised including intramolecular Diels-Alder methodology,[4] *o*-quinodimethane strategy,[5] chiral auxiliary induced asymmetric polyene cyclization,[6] Mukaiyama-Michael conjugate addition,[7] use of β-sulfonyl vinyl ketone,[8] in addition to Uskokovic approach[3] using a known asymmetric ketoacid.[9]

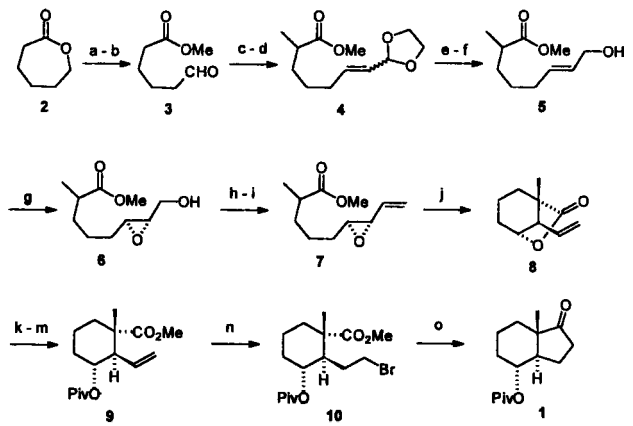


Scheme 1.

§This paper is dedicated to the 60th birthday of Professor Sang Chul Shim at KAIST.

Here we report a new enantioselective synthesis of functionalized *trans*-hydridanone **1**[10] based on the highly stereoselective epoxide cyclization reaction with carbanions.[11] Our synthetic plan is highlighted in Scheme 2.

The preparation of **7**, which served as the substrate for the intramolecular allylic epoxide cyclization was made starting from ε-caprolactone **2**. Saponification of ε-caprolactone followed by Swern oxidation[12] of the resulting ester alcohol afforded ester aldehyde **3** (77%). Two-carbon homologation to aldehyde functionality by Wittig reagent[13] gave **4** (79%) as a mixture of two isomers ((*Z*)-**4**:(*E*)-**4**=85:15). Methylation of this ketal ester **4** (61%) and subsequent ketal hy-



Scheme 2. (a) NaOMe, MeOH. (b) Swern oxidation. (c) (1,3-dioxolan-2-yl)methylenetriphenylphosphorane in DMSO, boiling THF. (d) LDA, THF; CH_3I, −78 °C. (e) 1 N HCl, THF. (f) $NaBH_4$, MeOH, 0 °C. (g) (−)-DET, $Ti(O\text{-}iPr)_4$, TBHP, 4 A° sieves, CH_2Cl_2, −23 °C. (h) Swern oxidation. (i) Ph_3PCH_3I, KHMDS, THF, −78 °C. (j) LDA, HMPA (0.3 eq.), THF, −78 °C to r.t.. (k) 1 N NaOH, MeOH. (l) CH_2N_2, ether. (m) pivaloyl chloride, DMAP (3 eq.), CH_2Cl_2. (n) HBr(g), 300 nm, *n*-pentane. (o) *t*-BuLi, THF, −78 °C.

drolysis using a diluted acid afforded *trans* enal, which was reduced with sodium borohydride to give allylic alcohol **5** (overall 85%). During deketalization by acid, complete isomerization to the desired *trans* geometry for the right stereochemistry in the following cyclization has been realized.

Sharpless epoxidation using (−)-diethyltartarate under a catalytic condition[14] was a highly enantioselective process which gave allylic alcohol **6** in 93% yield. Enantiomeric purity of **6** was found to be >99% determined by ^{1}H NMR analysis of its Mosher ester, which was prepared by Sharpless procedure[14] using (S)-(−)-Mosher salt. Swern oxidation of **6** and Wittig reaction of the resulting aldehyde gave the requisite allylic epoxide **7**[11] (overall 76%). Intramolecular regio- and stereoselective cyclization of **7** provided the desired cyclohexane system **8** (76%) with the *trans* stereochemistry of the vicinal vinyl and hydroxyl group. Saponification of **8** followed by treatment of the resulting acid with diazomethane[15] and pivaloylation of the alcohol group gave olefinic ester **9** in 86% overall yield.

Radical-initiated addition of HBr to the olefin functionality[16] gave primary bromide **10** (94%). Then the lithium anion initiated ring closure was set to produce the D-ring. In this reaction, the cooled (−78 °C) bromide solution was added dropwise to a cooled *t*-butyllithium solution in THF to afford *1* (71%). Thus, the whole process to the *trans* C/D-hydrindane ketone from ε-caprolactone gave a yield of 10.4% (15 overall steps).[17]

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17. Spectral data for **3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.77 (s, 1H), 3.66 (s, 3H), 2.51-2.25 (series of m, 4H), 1.75-1.54 (series of m, 4H). **4** (the major (*Z*)-isomer): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.55-5.37 (m, 2H), 3.92 (m, 4H), 3.66 (m, 3H), 2.43 (m, 1H), 2.15 (m, 2H), 1.78-1.28 (series of m, 4H), 1.13 (d, *J*=6.8 Hz, 3H). **5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.64 (m, 2H), 4.08 (m, 2H), 3.66 (s, 3H), 2.52 (m, 1H), 2.04 (m, 2H), 1.75-1.25 (series of m, 5H), 1.13 (d, *J*=6.8 Hz, 3H). **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.95-3.55 (series of m, 2H), 3.67 (s, 3H), 2.91 (m, 2H), 2.54 (m, 1H), 1.80-1.37 (series of m, 7H), 1.14 (d, *J*=7.0 Hz, 3H). $[\alpha]_D^{23}$=28.0° (c 1.37, $CHCl_3$).; its Mosher ester of (S)-(−)-Mosher salt; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.43 (m, 3H), 4.55 (dd, *J*=3.6, 12 Hz, 1H), 4.23 (dd, *J*=6.0, 13.2 Hz, 1H), 3.69 (s, 3H), 3.58 (s, 3H), 3.01 (m, 1H), 2.83 (m, 1H), 2.45 (m, 1H), 1.76-1.33 (series of m, 6H), 1.17 (d, *J*=8.0 Hz, 3H). **7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.52 (m, 2H), 5.25 (dd, *J*=2.7, 9.6 Hz, 1H), 3.67 (s, 3H), 3.09 (m, 1H), 2.81 (m, 1H), 2.45 (m, 1H), 1.75-1.37 (series of m, 6H), 1.15 (d, *J*=7.0 Hz, 3H). **8**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.33 (s, 1H),

5.27 (dd, J=1.8, 7.5 Hz, 1H), 4.64 (t, J=5.2 Hz, 1H), 2.78 (m, 1H), 1.87-1.47 (series of m, 6H), 1.07 (s, 3H). $[\alpha]_D^{23}=-30.9°$ (c 1.16, $CHCl_3$). mp 56-57 °C. **9**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.56 (m, 2H), 5.04 (s, 1H), 4.89 (m, 1H), 3.64 (s, 3H), 2.68 (t, J=9.8 Hz, 1H), 2.04-1.31 (series of m, 6H), 1.18 (s, 3H), 1.12 (s, 9H). $[\alpha]_D^{24}=+27.0°$ (c 1.13, $CHCl_3$). **10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.70 (dt, J=4.5, 10.6 Hz, 1H), 3.71 (s, 3H), 3.51 (m, 2H), 2.05 (m, 2H), 1.83-1.49 (series of m, 6H), 1.23 (m, 1H), 1.20 (s, 9H), 1.16 (s, 3H). **1**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.93 (dt, J=4.4, 10.5 Hz, 1H), 2.45 (m, 1H), 2.19-1.58 (series of m, 9H), 1.22 (m, 1H), 1.19 (s, 9H), 0.94 (s, 3H); IR ($CHCl_3$, cm^{-1}) 1737 (s), 1720 (s). $[\alpha]_D^{24}=+57.9°$ (c 1.04, $CHCl_3$). mp 54 °C.

Cation-π Interaction between Synthetic Hosts and Alkali Metal Cations

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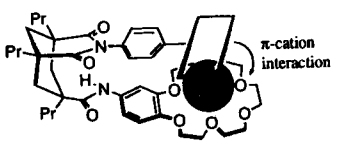
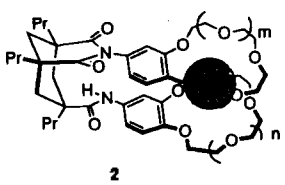
Among noncovalent binding forces, the cation-π interaction has recently received considerable attention because it plays an important role in biological systems such as acetylcholine-binding sites and ion channels.[1] A number of theoretical and experimental studies have been reported on the cation-π interaction between aromatic surfaces and quaternary ammoniums, or alkali metal cations.[2-5] Based on the computational calculations, Dougherty[3] and Kollman[4] described the nature and magnitude of the cation-π interactions between alkali metal cations and benzene. Experimentally, Shinkai[5] and Ungaro[6] have nicely demonstrated that two benzene rings of the 1,3-alternate calix[4]arenes can participate as π-donors in the complexation with metal cations, and thus increase the binding affinities and selectivities toward a particular metal cation.

We here report the synthesis and binding properties of the aryl-containing hosts **1** for evaluation of the cation-π interactions in the complexation with alkali metal cations in a water-saturated CH_2Cl_2.

The interaction between an alkali metal cation and aromatic surface alone is too weak in solution to be measured accurately. Therefore, the hosts **1** designed here are composed of two metal-binding sites, the benzo-18-crown-6 as a main binding site and the π-donor aromatic unit as an additional site. Two binding sites must be placed in a proper way to participate simultaneously in the complexation with metal cations. In addition, they must be conformationally independent of each other and thus the cation-π interactions could be deducted from the direct comparisons of the binding affinities of the reference host and aryl-containing analogues. For these purposes, tripropyl Kemp's triacid **4**[9,10] is an ideal spacer molecule in which carboxylic groups are separated ~3 Å from each other with U-shaped relationship.



1



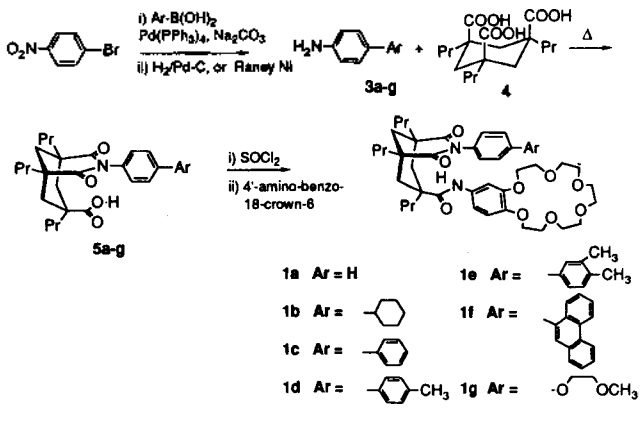
2

Utilizing this structural feature of Kemp's triacid **4**, we recently reported several bis(crown ether) hosts **2** in which two crown ethers could bind cooperatively alkali metal cations through intramolecular 1:1 sandwich-type complexes.[10a]

The synthesis of hosts **1a-1g** is outlined in Scheme 1. The various arylamines **3c-3f** were prepared by the Pd(0)-catalyzed coupling of 1-bromo-4-nitrobenzene with the corresponding boronic acids,[7] and followed by reduction with H_2/Raney Ni or Pd-C. A finely ground mixture of the arylamine **3** and tripropyl triacid **4** was heated at ~180 °C for 2 h under argon atmosphere to give N-aryl imide acids **5a-5g** (45-90%). After treating with $SOCl_2$, the acids were reacted with 4'-aminobenzo-18-crown-6 to afford the various hosts **1a-1g** (38-65%).[8]

The binding abilities of the hosts **1a-1g** toward alkali metal cations were determined by two phase (water/CH_2Cl_2) picrate extractions. The extraction experiments were performed at 26±0.2 °C by employing 5.0 mL of hosts (0.20 mM) in CH_2Cl_2 and 5.0 mL of picric acid (0.10 mM) and MOH (0.10 M) in deionized water, and the results are summarized in Table 1.

The host **1a** (Ar=H) has been studied as a reference



Scheme 1.