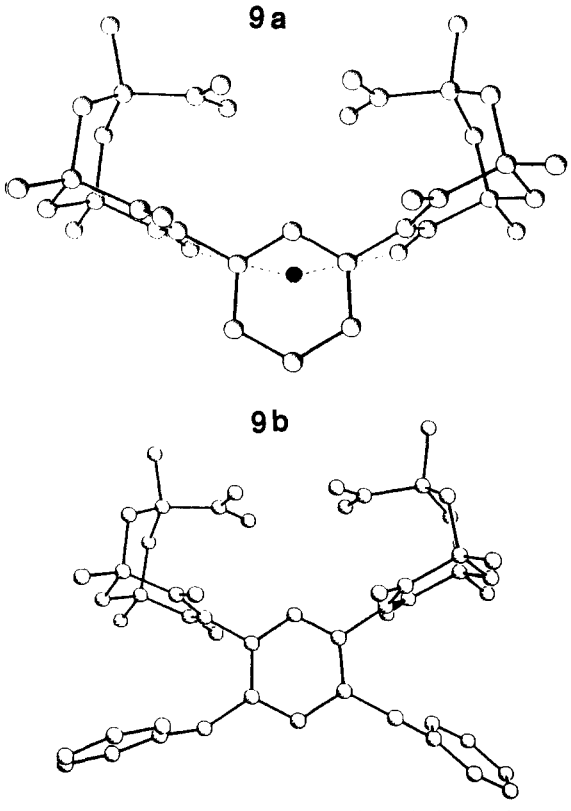

Figure 1. Crystal structures of dicarboxylic acids derived from **8a** and **8b**. In **9a**, a water molecule (●) is hydrogen bonded to two imide carbonyls and helps maintain the convergent conformation. All hydrogens have been omitted.

molecular hydrogen bonding can enforce the convergent conformation as evident in **9a** (the diacid derived from **8a**).

Several lines of evidence bear on the affinity of the new chelating agents for alkaline earth ions. First, the Δ pK_a observed[12] for the benzene derivative **4** (pK_{a1} = pK_{a2} = 11.1) suggests that dianions of the new structures provide an exquisite microenvironment for divalent ions. The diacid **9a** was sufficiently soluble in water to permit its evaluation as chelate under homogeneous conditions. With use of Ca^{2+} selective electrodes or pH titrations $K_a = 2.1 \times 10^5$ M^{-1} was measured for the diacid derivative **9a** with Ca^{2+}, assuming a 1:1 stoichiometry. This value might be compared to imidodiacetic acid,[13] for which $K_a = 7 \times 10^3$ M^{-1}.

The high lipophilicity of these systems permitted extraction of Ca^{2+} or Mg^{2+} from aqueous phases. For example, 0.1 M solutions of **4** in $CHCl_3$ were used to extract a solution of Ca^{2+} (59 ppm) and Mg^{2+} (24 ppm); >99% of the Ca^{2+} and 73% of the Mg^{2+} were removed from the aqueous phase. Parallel experiments with **9b** resulted in 97% removal of Ca^{2+} and 94% removal of Mg^{2+}.

Transport experiments using $CHCl_3$ between two aqueous solutions in a U-tube were also performed (Figure 2). The new carriers were comparable to A-23187 in their ability to transport Ca^{2+} across these model liquid membranes from a tris-buffered phase (pH = 9) to an acidic phase (pH = 1).

Finally, an ion exchange resin was prepared and tested. The dibenzyl pyridine derivative **9b** was adsorbed on unfunctionalized 4% cross-linked polystyrene by mere rotary evaporation of its $CHCl_3$ solutions in which the resin beads were suspended. About 0.4 mmol **9b** per gram could be attached in this fashion. The resin was capable of extracting calcium and magnesium ions from brine

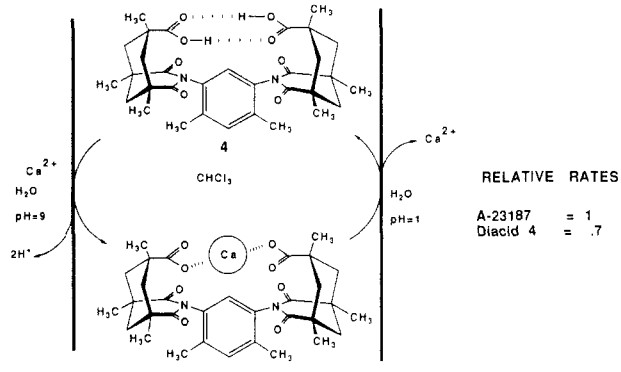

Figure 2.

solutions. At pH 12, with 1 equiv of Ca^{2+} in 0.1 M brine, about 20% of the sites bind Ca^{2+}, suggesting that stoichiometries other than 1:1 may be involved. Under conditions of 10-fold excess resin, the Ca^{2+} concentration in brine could be reduced from 2 ppm to <0.1 ppm. In these experiments, the polymer could be freed from metal ions by acid backwash.

In summary, a surprisingly effective, new class of chelating agents has been discovered. Their unique shapes enforce a trans relationship of the ligands in contact with the metal centers. It is likely that the catalytic behavior of metal ions bound by these new chelates will differ from ions in more conventional settings. We are exploring these possibilities and will report on them in due course.

Acknowledgment. This research was financed by Year Laboratories, Inc. The National Institutes of Health (GM 63239) supported the X-ray diffractometer used in these studies. We thank Professor Wm. Gordon for advice.

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Oxygenation of Hexafluorobenzene by Superoxide Ion

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The propensity of superoxide ion ($O_2^{\bullet-}$) in aprotic solvents to attack aliphatic and olefinic halocarbons via nucleophilic substitution is well documented,[1,2] and a recent report[3] establishes that this chemistry includes perchloroaromatic molecules. However, to date the C–F bond of fluorocarbons has been inert to $O_2^{\bullet-}$ (e.g., only the chlorine atoms of F_3CCCl_3 are displaced).[4] Here we report that perfluoroaromatic molecules [hexafluorobenzene

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Table I. Stoichiometries, Products, and Apparent Second-Order Rate Constants (k_1/[S]) for the Reaction of Excess Superoxide Ion ($O_2^{\cdot-}$) with Perfluoroaromatic Molecules in Dimethylformamide (0.1 M Tetraethylammonium Perchlorate) at 25 °C

substrate (S)[a]	$(E_{p,c})_S$, V vs SCE	$O_2^{\cdot-}$/S	products[b,c]	k_1/[S],[d] M^{-1} s^{-1}
C_6F_6	−2.0	2.0 ± 0.3	$F_5C_6OO^-$, F^-, O_2	3×10^1
C_6F_6 (large excess of $O_2^{\cdot-}$)		4.0 ± 0.4	$F_4C_4O_4^{2-}$, $2F^-$, $2O_2$	slow[f]
HC_6F_5	−2.3	2.0 ± 0.2	$HC_6F_4OO^-$, F^-, O_2	1×10^1
1,2,3,5-$C_6F_4H_2$	−2.5	2.0 ± 0.2	$H_2C_6F_3OO^-$, F^-, O_2	6×10^{-1}
1,2,4,5-$C_6F_4H_2$	−2.4			$<1 \times 10^{-2}$
$CF_3C_6F_5$	−1.7	2.0 ± 0.2	$CF_3C_6F_4OO^-$, F^-, O_2	1×10^2
$C_{12}F_{10}$	−1.8	4.0 ± 0.4	$C_{12}F_8(OO)_2^{2-}$, $2F^-$, $2O_2$	1×10^2
C_6Cl_6[e]	−1.5	12.0 ± 1.0	$6HOC(O)O^-$, $6Cl^-$, $4.5O_2$	1×10^3
CCl_4[e]	−1.1	5.0 ± 0.5	$HOC(O)O^-$, $4Cl^-$, $3.8O_2$	1×10^3

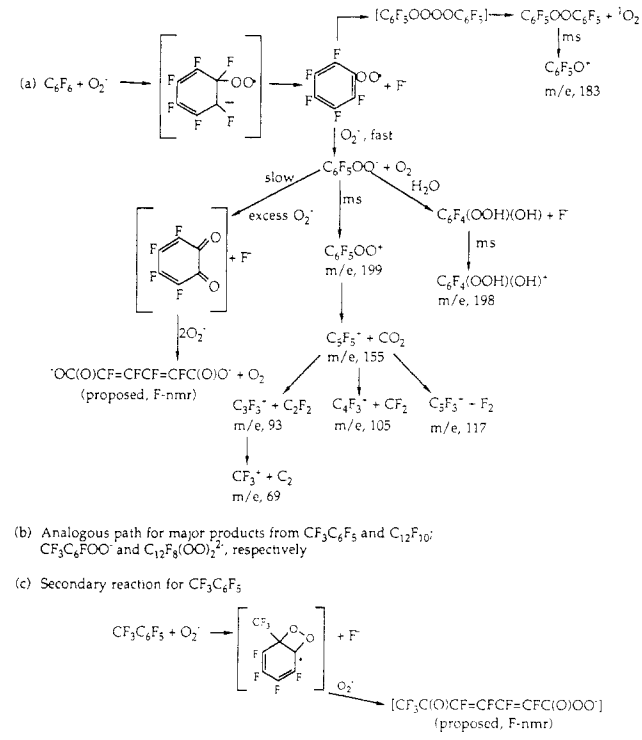
[a] Within 1 h $C_6H_3F_3$, $C_6H_4F_2$, and C_6H_5F do not react with $O_2^{\cdot-}$. [b] F NMR chemical shifts (intensity) in DMF-d_7 [relative to 1,1,1-trifluorotoluene; ppm], ortho (2F), meta (2F), para (1F): $C_6F_5O^-$, −105.5, −104.4, −125.5; product from C_6F_6 plus $2O_2^{\cdot-}$, −107.4, −107.1, −132.2. (The F–F splitting patterns for the two spectra are the same.) [c] Mass spectra (EI, *m/e*) for major product (separated by capillary GC) from the reaction of $2O_2^{\cdot-}$ per substrate. (a) C_6F_6: 199, 198, 183, 155, 117, 105, 93, 69 (interpreted in Scheme I). (b) $CF_3C_6F_5$: 249, 248, 233, 229, 205, 155, 117, 93, 69. (c) $C_{12}F_{10}$: 347, 346, 331, 303, 253, 165, 117, 93. [d] Apparent pseudo-first-order rate constants, k(normalized to unit substrate concentration [S]), were determined from the ratio ($i_{anodic}/i_{cathodic}$) for the cyclic voltammogram of O_2 in the presence of excess substrate, ref 7. Apparent rate constants are about 10 times smaller in acetonitrile. [e] Reference 3. [f] 2 h exposure.

(C_6F_6), perfluorotoluene ($F_5C_6CF_3$), and perfluorobiphenyl ($C_{12}F_{10}$)] undergo facile attack by $O_2^{\cdot-}$ in dimethylformamide (DMF) with the displacement of one fluoride ion and formation of an aryl peroxy radical (ArOO·) in the primary step.

The extent of the reactions for electrogenerated $O_2^{\cdot-}$ and $(Me_4N)O_2$[5] with perfluoroaromatic molecules has been determined by voltammetric assay of $O_2^{\cdot-}$ concentrations and their decrease in the presence of substrates. The reaction stoichiometries, product profiles, and apparent second-order rate constants for the combination of perfluoroaromatic molecules (and several hydro and dihydro derivatives) with excess superoxide ion in dimethylformamide are summarized in Table I.[6] Data for C_6Cl_6 and CCl_4 are included to emphasize the unique reactivity for the perfluoroaromatics. Prolonged exposure (2 h) of C_6F_6 to a large excess (10- to 20-fold) of $(Me_4N)O_2$ yields a symmetrical nonaromatic product with 4 fluoro groups (F NMR) that is a dicarboxylate.

The primary product from the combination of C_6F_6 with 2 equiv of $O_2^{\cdot-}$ is $C_6F_5OO^-$ on the basis of the F NMR spectrum of the product solution and the mass spectrum for the major peak from the capillary GC of the product solution (Table I). Similar analyses of the product solutions for the other fluoro substrates are consistent with a peroxide product from the displacement of a fluoride ion. A reasonable first step for these oxygenations is nucleophilic addition of $O_2^{\cdot-}$ to the polyfluoroaromatic (e.g., C_6F_6; Scheme I). Subsequent loss of fluoride ion will give an aryl peroxy radical, which will be reduced by a second $O_2^{\cdot-}$ to the aryl peroxide product. This reaction sequence (with the initial nucleophilic displacement the rate-determining step) is analogous to that observed for chlorohydrocarbons[4] and polychlorobenzenes.[3] However, the peroxo product of the latter systems is an effective nucleophile that attacks a second substrate molecule (or an adjacent aryl carbon–chlorine center). The stability of the $C_6F_5OO^-$ product indicates that it is unable to displace a fluoride from C_6F_6 or from an intramolecular process. As with other halocarbons,[3,4] the apparent rate constants for the initial step of the $O_2^{\cdot-}$/perfluoroaromatic reactions correlate with the reduction potentials for the substrates; the less negative the potential the greater the reactivity (Table I). Nucleophilic attack of C_6F_6 by ^-OH to give C_6F_5OH and F^- is a well-documented process.[8]

Scheme I



When $O_2^{\cdot-}$ (1.0 mM) is added to a large excess of C_6F_6 (200mM) in MeCN within the observation cell of a photoemission spectrometer,[9] an intense emission at 1.27 μm (characteristic of $^1O_2$ decay) is observed. Similar combinations of $O_2^{\cdot-}$ with excess CCl_4, CBr_4, $PhCCl_3$, and BuBr also result in a strong $^1O_2$-emission band.[10] With $PhCCl_3$ and BuBr, the $O_2^{\cdot-}$/excess-substrate combination dioxygenates singlet-oxygen traps (rubrene and diphenylbenzofuran) and yields $PhCCl_2OOCCl_2Ph$ and BuOOBu, respectively.[11] Hence, the $^1O_2$ emission from the $O_2^{\cdot-}/C_6F_6$ combination appears to result from an analogous mechanism [the dimerization of the primary product ($C_6F_5OO^{\cdot}$) to a tetraoxo intermediate and its subsequent homolytic dissociation to $^1O_2$ and $C_6F_5OOC_6F_5$ (Scheme I)]. The mass spectrum of the product solution exhibits a peak for a $C_6F_5O^+$ fragment (183 *m/e*, Scheme I).

In the gas phase (10^{-8} Torr, Nicolet Model 2000 FT-MS) $O_2^{\cdot-}$[12] also reacts with C_6F_6 via nucleophilic displacement to give $C_6F_5OO^{\cdot}$ and F^-, which parallels its ion–molecule chemistry with esters[12] and alkyl halides (CCl_4 and BuCl). Thus, Scheme I outlines a general mechanism with an initial nucleophilic attack by $O_2^{\cdot-}$ on an electrophilic aromatic carbon that is rate limiting and solvent dependent.

The facile reactivity of perfluoroaromatic molecules with $O_2^{\cdot-}$ to give peroxy radicals, peroxides, and $^1O_2$ may represent a mode of cytotoxicity for such materials that parallels that for halogenated hydrocarbons,[10,11] and C_6Cl_6 and polychlorobiphenyls (PCB's).[3,13,14]

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A Simple, Divergent, Asymmetric Synthesis of All Members of the 2,3,6-Trideoxy-3-aminohexose Family

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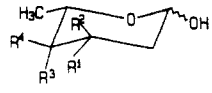
Several deoxyaminosugars constitute the glycosidic fragments of many anticancer antibiotics, such as anthracyclines,[1] glycopeptides,[2] and the recently reported esperamicin.[3] Interest in synthesizing these compounds, especially the 2,3,6-trideoxy-3-aminohexoses, has been apparent in the last 2 decades. More than 200 synthetic references relating to this subject were comprehensively reviewed in 1986.[1] A recent structure-activity study of antibiotics revealed the importance of aminosugars, for example, replacement of daunosamine (**1**) by acosamine (**2**) in daunorubicin

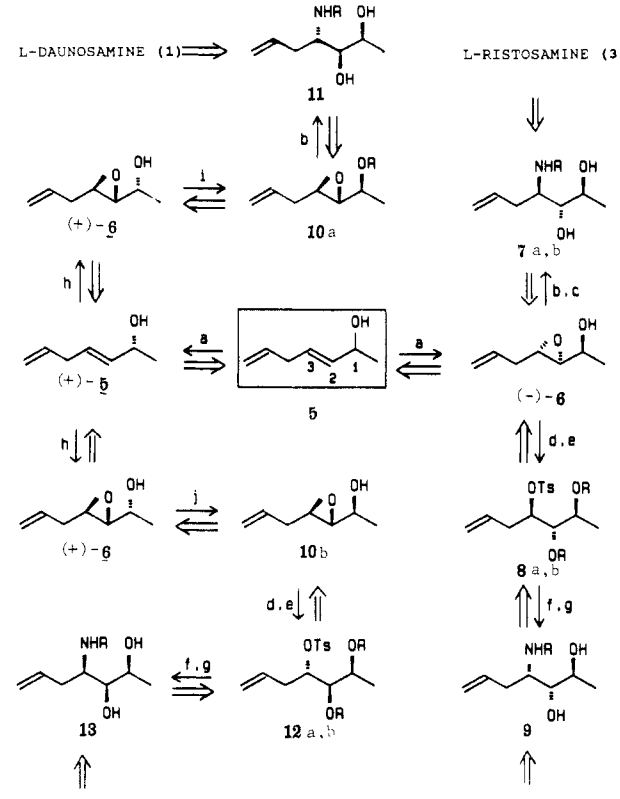


L-daunosamine (lyxo), R^2, R^4 = H; R^1 = NH_2; R^3 = OH, **1**
L-acosamine (arabino), R^2, R^3 = H; R^1 = NH_2; R^4 = OH, **2**
L-ristosamine (ribo), R^1, R^3 = H; R^2 = NH_2; R^4 = OH, **3**
L-3-*epi*-daunosamine (xylo), R^1, R^4 = H; R^2 = NH_2; R^3 = OH, **4**

and adriamycin produces analogues which are nearly devoid of cardiotoxicity but retain the anticancer activity.[4] Most of the syntheses of these aminosugars have been initiated from carbohydrate based materials and other natural chiral pools, but substantial efforts also have focused on the asymmetric synthesis from achiral compounds.[5,6]

We report here a simple, divergent synthesis of all four configurational isomers of 2,3,6-trideoxy-3-aminohexose (lyxo, arabino, ribo, and xylo) from the racemic 3,6-heptadien-2-ol. The synthetic strategy, depicted in Scheme I, relies mainly on the Sharpless epoxidation and a subsequent highly regiospecific ring-opening reaction. This strategy has been adopted by Masamune and Sharpless[7] as well as by Kishi[8] and by Roush[9] in the synthesis of monosaccharides. The crucial step here is installing the amino group with the right configuration to attain the three requisite contiguous chiral centers.

Scheme I. Retrosynthetic Analysis and Synthesis of L-2,3,6-trideoxy-3-amino-hexoses



[a] (a) Ti(O-*i*-Pr)$_4$ (0.14 equiv), L-(+)-DIPT (0.21 equiv, *t*-BuOOH (0.42 equiv), CH_2Cl_2, −25 °C; (b) NH_3–MeOH, 100 °C, 10 h; (c) PhCOCl, K_2CO_3, water–acetone; (d) PTS-LPTS, CH_2Cl_2, 0 °C; (e) cyclohexanone dimethyl ketal, CH_2Cl_2, PTS; (f) NaN_3/NH_4Cl, 100 °C, 15 h; (g) i, LAH, diethyl ether reflux, 1 h; ii, MeOH-H^+, 100 °C, 1 h; iii, PhCOCl, K_2CO_3, water–acetone; (h) Ti(O-*i*-Pr)$_4$, (1 equiv), D-(−)-DIPT (1.2 equiv), *t*-BuOOH (0.9 equiv), CH_2Cl_2, −25 °C; (i) PhCOOH, DEAD, Ph_3P, CH_2Cl_2; (j) i, *p*-NO_2-C_6H_4COOH, DEAD, Ph_3P, toluene, ii, MeOH/NaOMe, H^+.

Scheme I also presents synthetic details. Thus, kinetic resolution of the racemic **5** by the Sharpless method,[10] expeditiously afforded the epoxy alcohol (−)-**6** in 43.5% yield with more than 90% ee and the dienol (+)-**5** in 35% yield and 90% ee. Treatment of (−)-**6** with methanolic ammonia at 100 °C in a sealed tube, gave the required aminodiol, **7a** (R = H), which was converted to the known benzoylaminodiol **7b** (R = PhCO) [mp 137–138 °C, $[\alpha]_D^{10}$ −3.9° (*c* 1, EtOH) (lit.[5b,11] mp 137–138 °C $[\alpha]_D^{20}$ +6.4° (*c* 1, EtOH))] in 61% yield (two steps).[12] The observation that the ammonia opening occurred only at C_3 was not our expectation. In general, the nucleophilic opening of primary epoxyalcohols usually gives mixtures of products resulting from C_2 and C_3 attack, and high regioselectivity at C_3 can only be achieved with the aid of Ti(O-*i*-Pr)$_4$ or other chelating reagents.[13] Exclusive C_3 opening of (−)-**6** also occurred with NaN_3 to furnish the azido diol **14** (75% yield). **7b**, obtained in 60% yield by successive reduction and benzoylation of **14**, has been previously transformed to one of our targets, L-ristosamine (**3**).[11,12]

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