From Marco Polo to chiral stannanes - radical chemistry for the new millennium

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Dedicated to Don Cameron on the occasion of his retirement in recognition of his contribution to chemistry and the University of Melbourne

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Abstract

Over the past few decades, free-radicals have emerged as important intermediates in a large cross-section of disciplines ranging from chemical synthesis to biology and medicine. Free-radicals are now understood to be important in oxidative processes affecting areas that include materials science, DNA damage and heart disease, and are involved in many enzyme -mediated transformations. Significantly, radicals can be harnessed to provide powerful imaging tools and novel synthetic methodology with application to natural products and other chemistries. This review describes the author's involvement in the development of new free-radical technology useful for the preparation of compounds of biological importance. Examples include the use of carbon-centred radicals to prepare selenium-containing compounds that are then used as free-radical scavengers and antioxidants. Novel reagents have been developed to perform enantioselective free-radical chemistry with the aim of preparing novel pharmaceuticals. Examples are provided.

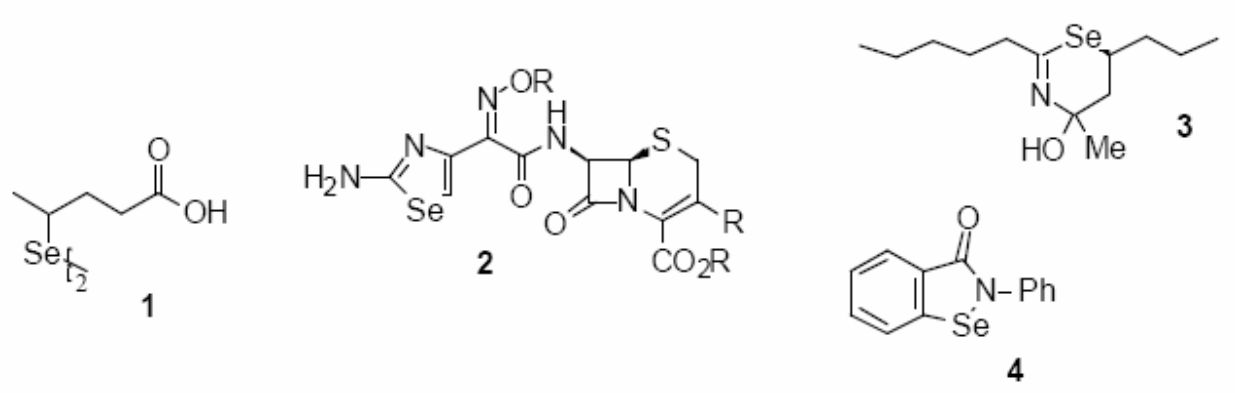
Keywords: Free radicals, antioxidants, selenium, tellurium, hemolytic substitution, chiral stannanes, enantioselective

Introduction

There can be no doubt that selenium-containing organic molecules have played and continue to play an important role in biology and medicine.[1] The mythology surrounding the "high toxicity"

of organic selenides, which itself can be traced to the voyages of Marco Polo,[2] and, more recently, the American Civil War,[3] has largely been dispelled, and a wide range of organic selenides are now accepted as useful antioxidants,[4] antiinflammatory agents,[5] antibiotics[6] and anti-viral agents.[7] Examples include the diselenovaleric acid **1** which provides an effective treatment for Kwashiokor, a protein-malnutrition disorder,[8] selenacephalosporins **2** which were patented by Hoffman La Roche as antibiotics,[9] selenazine **3** which is reported to be effective against Methicillin Resistant *Staphylococcus aureus*,[6] (MRS) and Ebselen **4**, which has been evaluated in clinical trials as a non-steroidal antiinflammatory.[5]

It is well established that selenium is an essential trace element and selenium dietary supplements are commonly available, especially in countries such as France and New Zealand, where soils are selenium deficient.[10] The principal role of selenium *in vivo* is to prevent free-radical damage either through incorporation into radical scavengers, or indirectly through reduction of the byproducts of oxidative damage.



In recent years there has been a rapid rise in interest in the area of antioxidant chemistry. "Free radicals are bad -antioxidants are good" appears to be the message driven to customers of companies that produce and/or supply antioxidant dietary supplements, cosmetics and related consumer products. Who is now not aware that both red wine and tea are "rich in antioxidants" and that some antioxidant containing cosmetics "stop the visible signs of aging"? Is it really the case that all free-radicals are bad? And what of the fate of the radical products of oxidation processes?

Work in our laboratories has demonstrated that free-radicals can be harnessed to provide beneficial products and chemical technologies. This paper highlights some of our recent quests for the Holy Grail† of free-radical chemistry and includes the preparation of selenium-containing antibiotics, carbohydrates, antioxidants and anti-inflammatory agents and the development of reagents for use in enantioselective synthesis.

† The legend of the Holy Grail is one of the most enduring in Western European literature and art. The Grail was said to be the cup of the Last Supper and at the Crucifixion to have received blood flowing from Christ's side. It was brought to Britain by Joseph of Arimathea, where it lay hidden for centuries. The search for the Grail became the principal quest of the knights of King Arthur. It was believed to be kept in a mysterious castle surrounded by a wasteland and guarded by a custodian called the Fisher King, who suffered from a wound that would not heal. His recovery and the renewal of the wastelands depended upon the successful completion of the quest. Equally, the self-realization of the questing knight was assured by finding the Grail.

Discussion

Ebselen and the quest for selenium-based radical scavengers

Glutathione peroxidase (GSH-Px) is a mammalian selenoenzyme that catalyses the reduction of a wide variety of hydroperoxides which are known to generate highly-reactive oxygen radicals that destroy key biological molecules and cause damage to cell membranes.[11] The activity of GSH-Px is principally due to the redox chemistry surrounding the selenocystine residue found in the active site of the enzyme.[11]

Ebselen (2-phenyl-1,2-benzisoselenazol-3(*2H*)-one), **4** and some of its derivatives mimic the action of GSH-Px.[11] The sulfur analogue is completely inactive, an observation which highlights the importance of selenium in this redox chemistry.[12] Ebselen has also been shown to be a nitric oxide synthase (NOS) inhibitor,[13] to induce cytokines such as interferons, tumour necrosis factor, interleukin-2 and gratunocytemacrophage colony stimulating factor.[14] These properties combined with Ebselen's low toxicity have led to interest in its therapeutic potential for a number of diseases.[5]

Fong demonstrated some time ago that Ebselen and analogues could be prepared in good yield through the use of free-radical homolytic substitution chemistry.[15] Interestingly, attempts to prepare the N-acyl pyridinethiooxycarbonyl (PTOC) carbamate precursor resulted in the formation of the rare benzoselenazine-2,4-dione ring system **5** (Scheme 1).[16] We reasoned that since compounds **5** resemble Ebselen, their pharmacology should be assessed. Indeed, Venn demonstrated that **5** is an NOS inhibitor, but less effective than either Ebselen **4** or nitro-L-arginine, a commonly used (standard) inhibitor (Figure 1).[17]

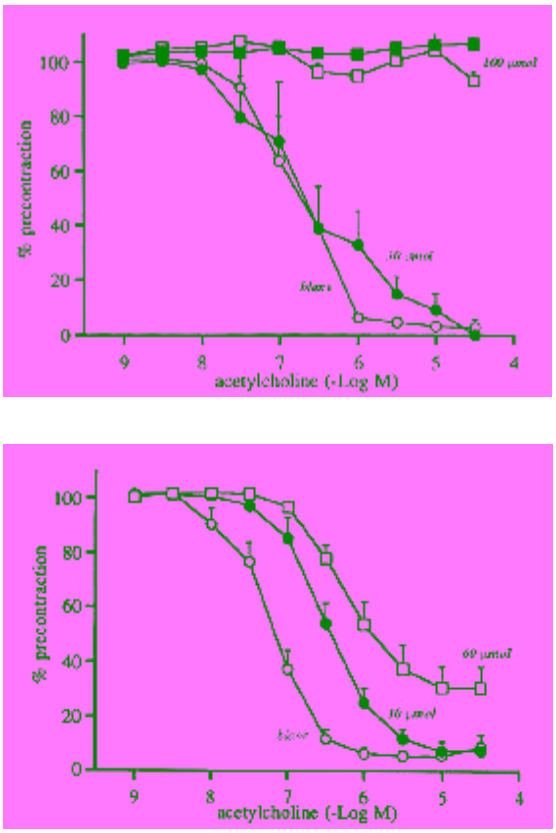
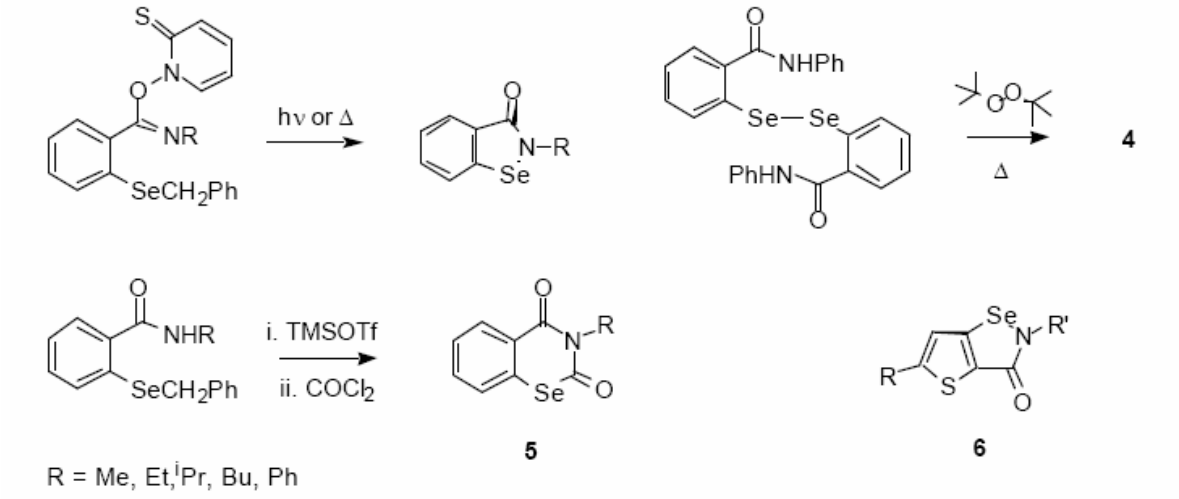


Figure 1. Bioassay of endothelial NOS (eNOS) stimulated by acetylcholine, that produces nitric oxide NO and relaxes rat isolated aorta. Nitro-L-arginine (top left), Ebselen (top right) and **5** (R = Bu) (below).

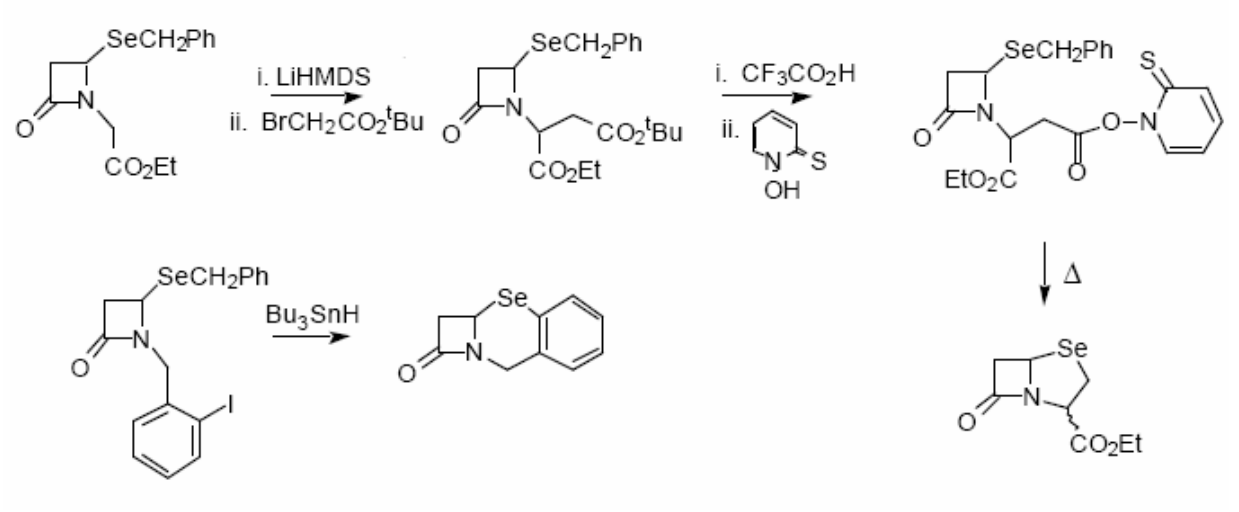


Scheme 1

The chemistry described above has also been applied to the preparation of thiophene analogues **6** of Ebselen which are expected to show improved solubility properties.[18]

Antibiotics for the Fisher King† -toward selenium-containing penems and cephalosporins

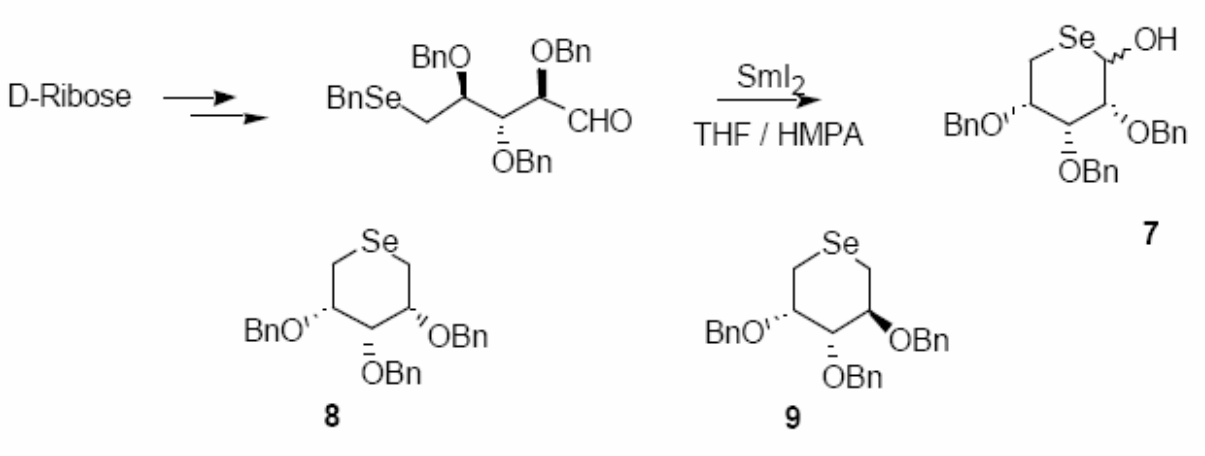
It is generally appreciated that β-lactam based antibiotics have a limited future given increased resistance demonstrated by many strains of bacteria. There is an urgent need for the development of new classes of antibiotic and many laboratories have made significant progress in this area, especially with the introduction of peptide-based agents. As part of ongoing work, Martin and Carland explored methods of incorporating selenium into the penem and cephalosporin nuclei.[19] Once again, free-radical homolytic substitution was used to effect the required outcome; examples are given in Scheme 2.



Scheme 2

A crusade for start of the new millennium -novel antioxidant carbohydrates

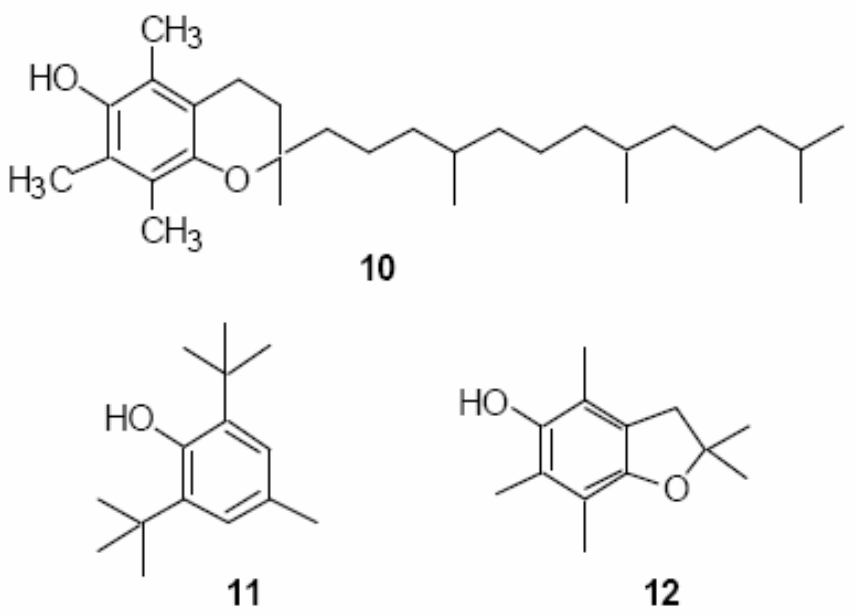
There is a need for the development of improved, water-soluble antioxidants. As part of an ongoing collaboration with the Heart Research Institute in Sydney, we have been interested in selenium and tellurium containing carbohydrates. It is interesting to note that most organic selenides tested *in vitro* have proven to be effective antioxidants, while the few organic tellurides tested have proven to be more effective still.[20] Zheng utilised samarium iodide mediated homolytic substitution chemistry to prepare selenium derivatives (eg. **7**) of arabinose, ribose and xylose, while Lucas and Nguyen were able to prepare selenium and tellurium derivatives (eg. **8**, **9**) of the analogous deoxysugars (Scheme 3).[21]



Scheme 3

Have we found the Holy Grail? Selenium and tellurium analogues of Vitamin E.

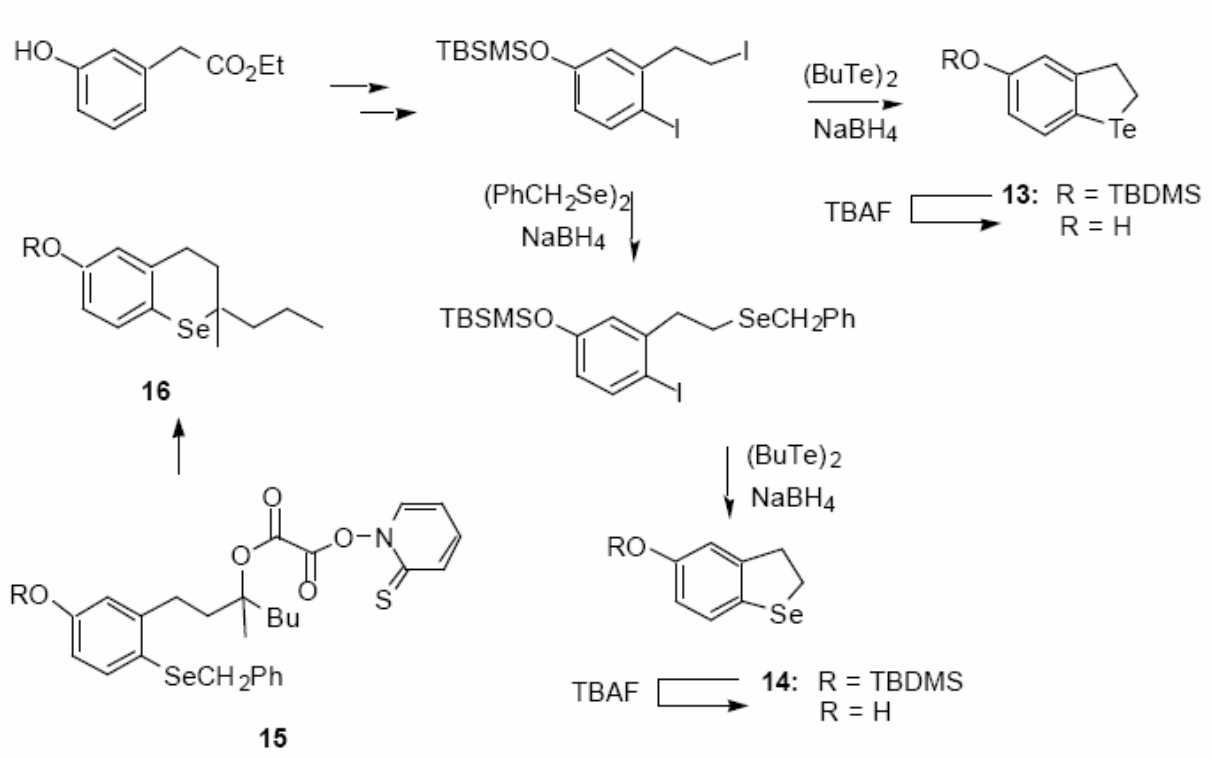
α-Tocopherol **10** is a lipid-soluble antioxidant present in human blood and the major component of Vitamin E.[22] The activity of **10** is most likely due to its ability to quench active peroxyl radicals *in vivo* through the rapid transfer of its phenolic hydrogen.[23] 2,6-Di-*tert*-butyl-4-methylphenol (BHT) **11** is a further example of a common antioxidant which finds application in the food industry.[24]



Benzofuran **12** displays enhanced antioxidant activity when compared with **10**; this enhanced activity has been explained in terms of the better overlap between the non-phenolic 2p-type lone

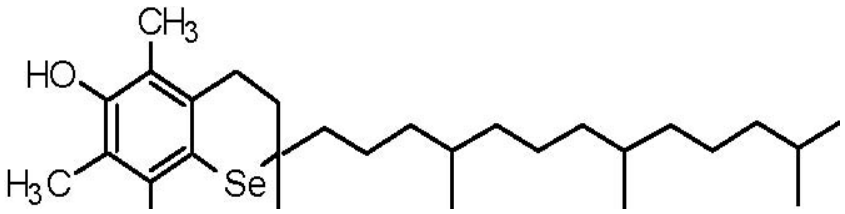
pair and the aromatic π-system in **12** as compared to **10**.[25]

As part of ongoing collaboration with the research group of Engman in Sweden, we have been involved in the application of the novel free-radical chemistry developed in our laboratories at the University of Melbourne to the preparation of selenium- and tellurium-containing tocopherol analogues with enhanced antioxidant capacity.



Scheme 4

The serendipitous discovery by Laws and Zugaro that butyltelluroate is an effective electron transfer agent has been put to good use in the preparation of benzotellurophenes **13** and benzoselenophenes **14**.[4] In addition, Malmström was able to show for the first time that tertiary carbon-centred radicals generated from PTOC oxalyl esters **15** undergo smooth homolytic substitution chemistry to provide antioxidants **16** in good yield (Scheme 4).[26] Current efforts are directed toward the preparation of selenotocopherol **17** which effectively combines the antioxidant capacities of both hindered-phenol and selenide moieties into the same molecule.



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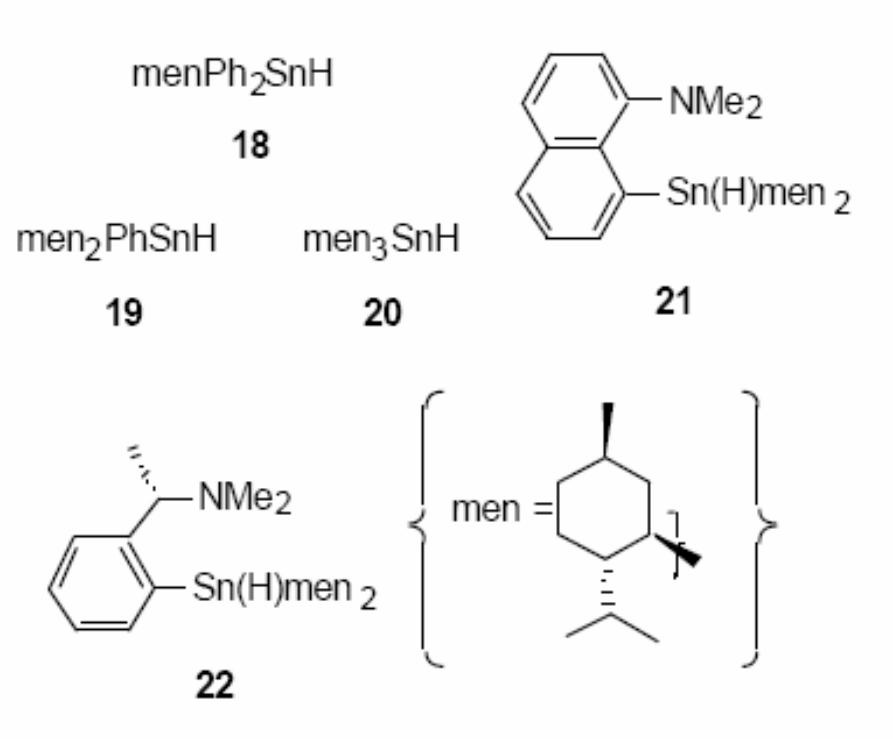
Drinking from the Cup - enantioselective free-radical chemistry

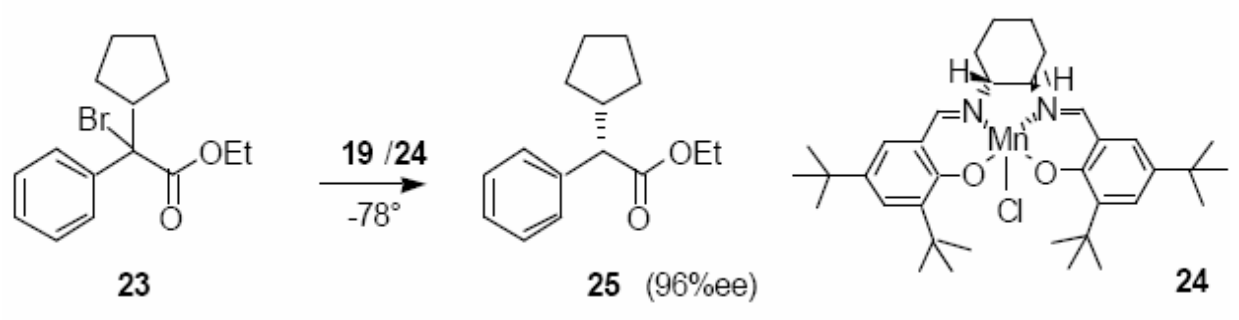
More than 90% of biomolecules exhibit chirality. Many pharmaceutical products contain different chiral forms of drugs, some of which are harmful or ineffective. For example, one form of the drug naproxen has 28 times the anti-inflammatory activity of its enantiomer. In the synthetic form of dopamine used to treat Parkinson's disease one isomer acts on the nerve cells to control the patient's tremors whilst the other enantiomer is toxic.

The technology of chiral synthesis, known as chirotechnology, is an industry rapidly increasing in commercial importance. Growth continues in both the number and value of single enantiomer drugs. In 1992 chiral pharmaceuticals alone were estimated to have a market value of $US18 billion. This year they are worth over $US100 billion.[27] The basis of the chirotechnology industry is the preparation of products in a single pure chiral form; 80 per cent of new drugs entering development are enantiomerically pure. The development of improved methods to provide single-enantiomer compounds is therefore a topical objective.

A significant challenge facing free-radical chemists is in the area of stereocontrol, specifically the ability to control the direction of reagent attack at a prochiral radical. Despite there being numerous reports of free-radical reactions proceeding with diastereocontrol, there are very few examples that proceed with genuine enantiocontrol.[28] The majority of this small set of examples involve the use of chiral auxiliaries.[28] Of the remaining few reports, the introduction of asymmetry in the substrate through the use of chiral Lewis acid mediation,[29] and in the reagent through the use of chiral ligands on the tin atom in suitably constructed stannanes,[30] have been the methods of choice for achieving enantioselectivity in radical chemistry. Our approach to the development of synthetically useful chiral stannanes primarily involves the judicious choice of ligand from the multitude of compounds available in the natural chiral pool.

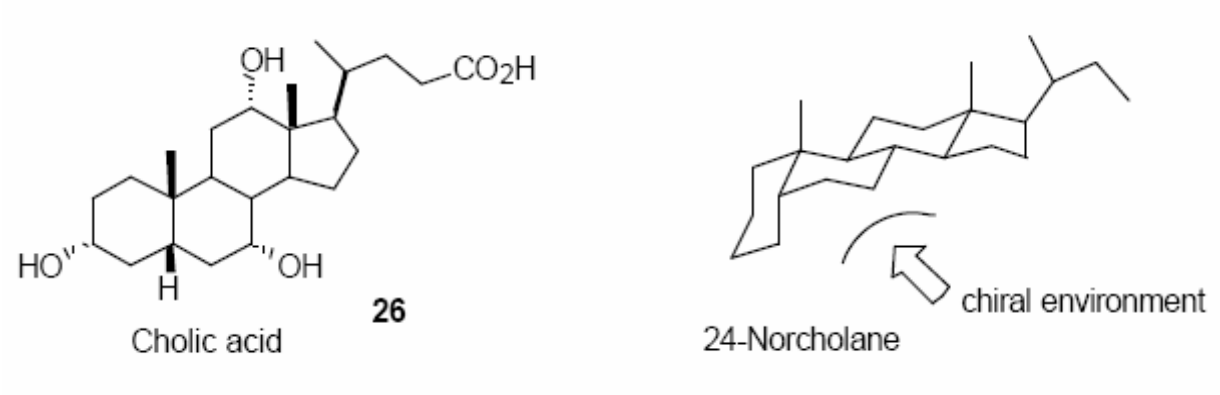


Work carried out in our laboratories over the past three years and in conjunction with the research group of Dakternieks at Deakin University has been directed toward the development of novel enantiomerically pure stannanes for use in free-radical reduction chemistry. To that end Dunn prepared a series of menthyl-substituted stannanes **18** -**20** and some others derived from aromatic amines (eg. **21**, **22**).[31,32] Perchyonok tested these reagents against a series of substrates while Henry modelled the reactions in question through the use of *ab initio* molecular orbital theory.[33]

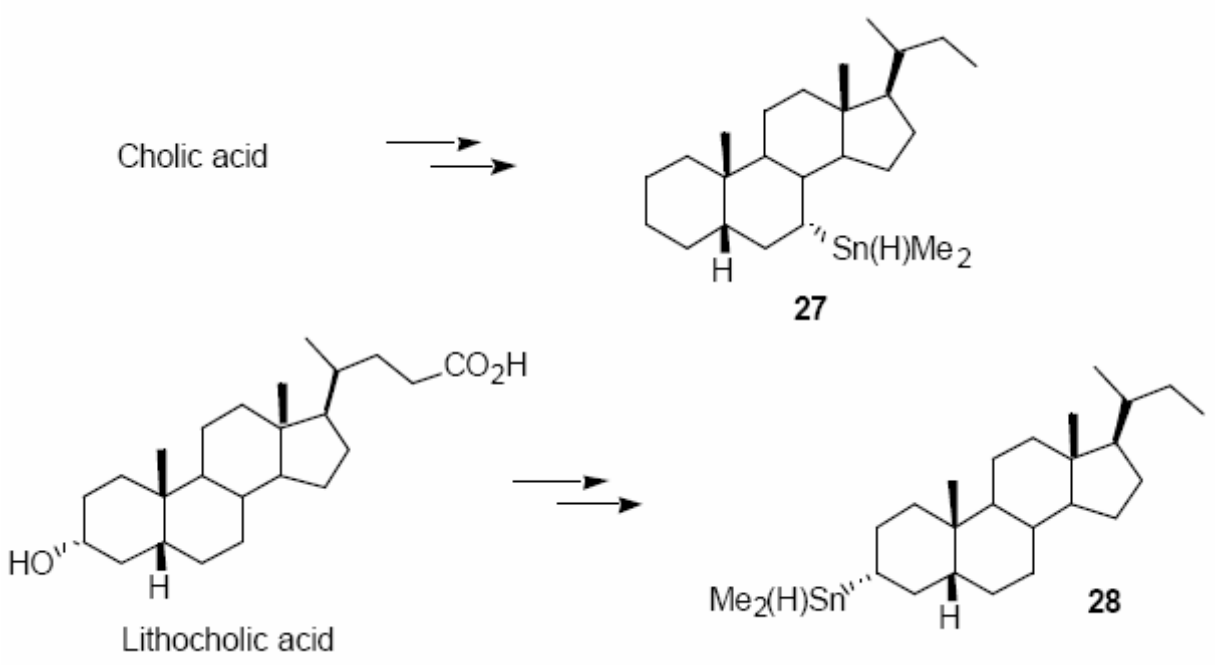


Scheme 5

Perchyonok also demonstrated that dimenthylphenyltin hydride **19** reacts with bromide **23** in toluene at -78° and in the presence of (*S*,*S*)-(+)-N,N'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride **24** to afford ethyl (*S*)-2-phenyl-2-cyclopentylacetate **25** with 96% ee (Scheme 5).[34] To the best of our knowledge, this result represents the highest-ever reported enantioselectivity observed during any organic free-radical transformation. More extensive enantioselectivity data can be found in our recent publication.[34]



Molecular modelling has also played an important role in the design of novel reagents. Skidmore showed recently that cholic acid **26** provides an excellent chiral template for stannane-based reagents. Indeed, computational data recommended **27** and **28** as the reagents of choice for enantioselective reduction; these stannanes were subsequently prepared from cholic acid and lithocholic acid (Scheme 6).[35]



Scheme 6

In practice, the 7α-stannane **27** afforded enantioselectivities in excess of 90% in several reactions,[36] providing strong support for our approach involving the combination of molecular modelling and experimental techniques.

A renaissance in radical chemistry - concluding remarks

During the twenty year period 1970 – 1990, free-radical chemistry underwent a series of remarkable transformations that effectively drew to a close the era in which free-radicals were considered to give rise only to intractable tars or polymers. The increased understanding of the factors which govern the reactivity, regio-and stereochemistry of radical addition chemistry led to the emergence of a maturity which saw the development of several impressive syntheses based on radical chemistry. While this period revolutionised synthetic chemists' attitudes toward free-radicals, in 1990 there were still some limitations confronting free-radical chemistry that required attention. These included, most notably, a lack of methods for the formation of bonds to higher heteroatoms, and the low levels of stereochemical control achievable in radical transformations. Work in the author's laboratories at The University of Melbourne over the last decade has seen significant inroads in both of these areas. New reagents and methods for the preparation of novel selenium and tellurium containing compounds of interest in biology and medicine have been developed and utilised, while novel reagents that control hydrogen transfer reactions (homolytic substitution at hydrogen) have been developed to the extent that single-

enantiomer outcomes are now possible. These discoveries have been applied to the preparation of novel antioxidants, antibiotics, free-radical scavengers, nitric oxide synthase (NOS) inhibitors as well as enantiopure intermediates for use in the pharmaceutical industry.

In much the same way that a clearer understanding of the details of homolytic addition chemistry gave rise to a rapid increase in the use of that methodology in synthesis, recent increases in the understanding of homolytic substitution processes have the similar potential of providing chemists with yet further tools for their synthetic endeavours.

Acknowledgements

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