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**Stereoselective Synthesis (Part E)**

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*This volume is dedicated to  
Prof. H.C. Brown  
in appreciation of his monumental  
contributions in the field of  
chemistry*

## PREFACE

The eighth volume of Professor Atta-ur-Rahman's Studies in Natural Products Chemistry series constitutes a pleasant potpourri of diverse offerings of topics on naturally occurring substances. Several contributors focus on singular reactions for the synthesis of structurally complex natural products. Thus Krief presents intriguing reactions of selenides with organolithium reagents for the synthesis of terpenes, especially those containing neighboring quaternary carbon centers. McMurry portrays the use of his invention, the low-valent titanium-mediated carbonyl coupling reaction, in the construction of cembranic diterpenes. The Diels-Alder reaction with chiral dienophiles is the center of attraction of Helmchen syntheses of cyclopentanoid natural systems. Electrochemical phenol oxidations lead Shizuri in few steps to neolignans and sesquiterpenes. Macrocyclic terpene syntheses by way of known intramolecular displacement reactions are the concern of Takahashi as well as Oehlschlager. Vedejs exhibits the build-up of medium-sized, functionalized carbocycles and heterocycles via ring expansion involving an array of versatile sulfur compounds. Various manipulations of neighboring tricarbonyl compounds permit Wasserman to synthesize  $\beta$ -lactam antibiotics, isoquinoline, indole and Erythrina alkaloids and pyrrole pigments. Palladium-induced cyclization of enynes enables Trost to build up structurally complex polycycles and natural products therefrom. Consecutive Michael condensations guide Spitzner to bicyclo[2.2.2]octane-bearing terpenes.

Syntheses by more general means are exemplified by those of the bisabolenes (Kreiser), prenyl glycosyl pyrophosphates (Danilov and Shibaev), gibberellin interconversions (Adam), indole alkaloids (Szantay), thiooligosaccharides (Defaye), cyclo-L-rhamnohexaose (Nishizawa) and carcinogenic DNA adducts (Johnson). Voelter guides us through the maze of polypeptide synthesis in his construction of the thymosins, while Basha introduces the medicinal chemistry of norepinephrine and its analogues.

Finally, we are treated to a pleasant interlude of biosynthesis by Kirby's description of the enzymic methylmuconate interconversions and to organoborane chemistry by Brown's stroll through his life-long contributions to this field. It is a joy to feast one's eyes through the pages of the book.

Ernest Wenkert

La Jolla, California, U.S.A.

January 1991



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## CONTENTS

Foreword	vii
Preface	ix
Contributors	xv
Original synthesis of molecules containing adjacent quaternary carbons A. KRIEF, J.-L. LABOUREUR, M. HOBE AND PH. BARBEAUX	3
Cembrane diterpene synthesis using titanium-induced carbonyl coupling reactions J.E. McMURRY AND R.G. DUSHIN	15
Terpene synthesis E. WENKERT	33
Synthesis, relative and absolute configuration of some natural bisabolones W. KREISER	39
Phosphopolyprenols and their glycosyl esters: chemical synthesis and biochemical application L.L. DANILOV AND V.N. SHIBAEV	63
New aspects in synthesis of gibberellins G. ADAM, B. VOIGT, M. LISCHESKI, A. SCHIERHORN, A. PREISS AND L. KUTSCHABSKY	115
Cyclopentanoid natural products via asymmetric Diels-Alder reactions G. HELMCHEN, A. GOEKE, S. KREISZ, A. KROTZ, G.H. LAUER AND G. LINZ	139
Total synthesis of natural products by using anodic oxidation of phenols as a key step Y. SHIZURI, H. SHIGEMORI, K. SUYAMA, K. NAKAMURA, Y. OKUNO, M. OHKUBO AND S. YAMAMURA	159

Natural products syntheses by using macrocyclically controlled reactions T. TAKAHASHI	175
Heteroatom mediated synthesis of large ring compounds E. VEDEJS	205
Occurrence and synthesis of macrocyclic semiochemicals E. CZYZEWSKA AND A.C. OEHLISCHLAGER	219
Application of the chemistry of vicinal tricarbonyl compounds in the synthesis of products of biological interest H.H. WASSERMAN AND C.B. VU	261
Cycloisomerization of enynes as a valuable tool for the synthesis of natural products B. M. TROST	277
Synthetic studies in the alkaloid field F. SOTI, M. INCZE, ZS. KARDOS-BALOGH AND Cs. SZANTAY	283
The methylmuconate pathways, stereochemistry and mechanism of enzymic reactions G.W. KIRBY AND R.B. CAIN	295
Thio-oligosaccharides: their synthesis and reactions with enzymes J. DEFAYE AND J. GELAS	315
A metal-free thermal glycosylation and synthetic study of cyclo-L-rhamnohexaose, the first L-cyclooligosaccharide M. NISHIZAWA	359
Synthesis and chemistry of carcinogenic adducts of DNA F. JOHNSON	373
Novel conformationally restricted analogs of norepinephrine: synthesis and structure activity F.Z. BASHA	395
Sequential Michael additions in the synthesis of natural products D. SPITZNER	409

Strategies for the total syntheses of thymosins  
W. VOELTER AND A. KAPURNIOTU

433

Asymmetric synthesis via chiral organoboranes - an  
unexpected bonus from a half - century of borane research  
H.C. BROWN

463

Subject Index

479

## Stereoselective Synthesis





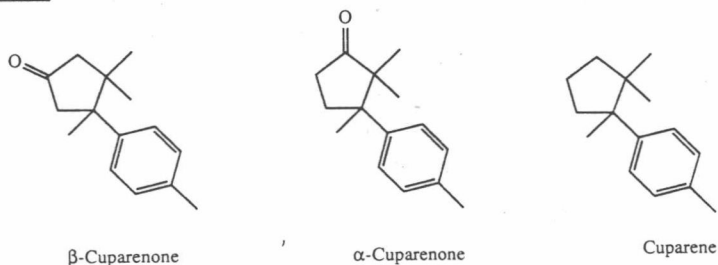
## Original Synthesis of Molecules Containing Adjacent Quaternary Carbons

Alain Krief, Jean-Louis Laboureux, Myriam Hobe and Philippe Barbeaux

The construction of a quaternary carbon still remains a challenge. This is particularly the case when this carbon has to be formed next to another quaternary centre. Not only problems inherent to the steric bulk around the reactive sites but also stereochemical problems have to be solved. Two original solutions to this problem are described in this article.

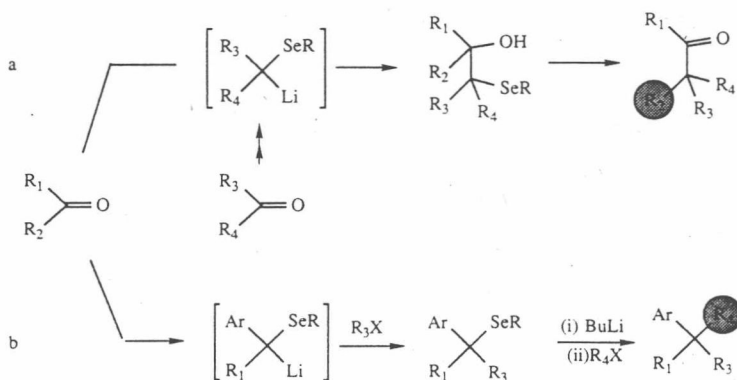
The synthesis of compounds bearing a quaternary carbon is often a difficult task (ref. 1) but the construction of molecules containing adjacent quaternary centers still remains a challenge. We have ourselves described over the past decade two different solutions to that problem which culminated with various syntheses of (d,l)- $\alpha$ - and  $\beta$ -cuparenones (ref. 2) and (d,l)-cuparene which possess two adjacent quaternary centres and which are the main constituents of the essential oil of *Thujia orientalis* (Scheme 1).

Scheme 1



Both approaches which we have developed involve carbonyl compounds as the starting materials and  $\alpha$ -selenoalkyl- or  $\alpha$ -selenobenzylolithiums as the key intermediates (ref. 3) (Scheme 2).

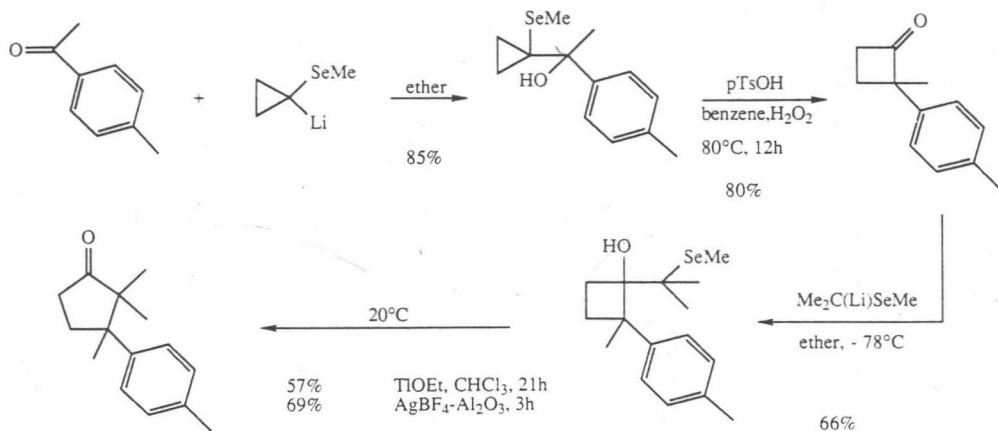
Scheme 2



The first approach (Scheme 2 entry a) employs the reaction of these particularly nucleophilic organometallics with carbonyl compounds and leads to  $\beta$ -hydroxyalkyl selenides (refs. 2-4, 6-20) even from the highly enolisable deoxybenzoine (ref.7) or the highly hindered ketones such as 2,2,6,6-tetra methyl cyclohexanone (refs. 8,9a), 2,2,6-trimethyl cyclohexanone (refs. 8,9a) and di-tert-butyl ketone (ref. 9a) Further reaction of these pinacol-type derivatives, which possess two alkyl groups at the carbon bearing the seleno moiety, with soft electrophiles which can interact selectively with the soft selenium atom, such as (i) silver tetrafluoroborate ( $\text{AgBF}_4\text{-Al}_2\text{O}_3$ ,  $\text{CHCl}_3$ , 20 or 60°C, 2 to 8 h (conditions Ag)) (ref.10,13) or (ii) dichlorocarbon generated from chloroform and (a) thallous ethoxide (refs. 12-19) [5.6 equiv.,  $\text{CHCl}_3$ , 20°C, 10-20 h (conditions Tl)] or (b) potassium hydroxide under phase transfer conditions (refs. 13,14) [10 % aq. KOH,  $\text{CHCl}_3$ , cat.  $\text{PhCH}_2\text{NEt}_3\text{Cl}$ , 20°C, 1-2 h (conditions PTC)] produce homologated carbonyl compounds (refs. 9,10,12-20) (Scheme 2a). The whole process involves the insertion of a ketone in between the carbonyl group of aldehydes and ketones and their alpha carbon and thereby allows the ring enlargement of cyclic ketones.

It allows the synthesis of (d,1)- $\alpha$ -cuparenone (ref. 2) from p-methyl acetophenone and acetone (the precursor of 2-lithio-2-methylselenocyclopropane) (Scheme 3). It is interesting to notice that the rearrangement of the  $\beta$ -hydroxyalkyl selenide intermediary formed from 2-methyl-2-p-tolyl cyclobutanone and the  $\alpha$ -selenoalkyllithium derived from acetone, takes place selectively by migration of the most alkyl-substituted carbon, a behaviour quite generally observed with related  $\beta$ -hydroxyalkyl selenides.

Scheme 3



It also allows (ref. 20) the synthesis of permethyl cyclopentanone and permethyl cyclohexanone via an iterative process which implies the insertion of the hydrocarbon framework of acetone in between the carbonyl group of permethyl cyclopentanone respectively and their alpha carbon (Scheme 4).