The Concept of Transient Chirality in the Stereoselective Synthesis of Functionalized Cycloalkenes Applying the Retro-Diels–Alder Methodology

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Contents

I. Introduction

Stereochemical control is an essential feature of the synthesis of organic molecules containing stereogenic elements. The demand for synthetic methodology with a high degree of stereocontrol has had a major impact on the development of synthetic organic chemistry during the past decade.[1] To achieve stereoselectivity, two distinct processes can be distinguished: addition to a stereoheterotopic face of a π-system and selective modification or replacement (substitution) of stereoheterotopic ligands. In chiral systems, the elaboration of further stereogenic centers is usually mainly determined by the restriction in conformational freedom imposed by the core structure together with sufficient degree in dissymmetry of the reaction sites. The difference in free energy associated with the diastereomeric transition states or products ultimately determines the stereochemical outcome of such reactions. In prochiral structures, the stereoselective formation of a new stereogenic center requires reagents that are chiral, either intrinsically or as a consequence of noncovalent interactions with a chiral surrounding. Although considerable progress has been made in this area of enantioselective synthesis, the extent of stereoselectivity is generally highly substrate dependent.

During the past decade, considerable effort has been made to find stereoselective routes to functionalized cyclopentenones and cyclopentanones as these structural entities form an essential part of many biologically interesting compounds. In particular, the discovery of prostaglandins, e.g., prostaglandin A_1 **1**, in the early 1960s and the recognition of their pharmacological importance as essential human fatty hormones that control a multitude of important physiological processes has initiated research in this area. Later, other biologically interesting cyclopentenoids were discovered which possess antibiotic and/or antitumor activity. Examples are kjellmanianone **2**, sarkomycin **3**, methylenomycins A **4** and B **5**, pentenomycin **6**, and a series of marine eicosanoids related to prostaglandins, such as clavulones **7**, punaglandins **8**, and halovulones **9**, Figure 1. However, most attempts to find general routes to these molecules met only with limited success as the starting substrates or the desired products were generally kinetically too labile to be handled or the stereoselectivity attained was not satisfactory.

When we entered this field of cyclopentenoid chemistry, we considered the chemical transformation of appropriately functionalized cyclopentadienones **10**, for example, by conjugate addition of suitable nucleophiles followed by electrophilic trapping of the enolate as a conceivable and most direct route to functionalized cyclopentenoids **11** (Scheme 1). Clearly, the use of a chiral auxiliary present either in the cyclopentadienone or the reagents would be required to introduce the first stereogenic center in a stereoselective manner. Unfortunately, this approach did not appear to be feasible as cyclopentadienones **10** are generally highly reactive molecules which rapidly dimerize at temperatures above −100 °C. An elegant solution to this problem is the use of the *endo*-tricyclo[5.2.1.$0^{2,6}$]decadienone system **12** which in essence is a Diels−Alder product of cyclopentadiene or furan and cyclopentadienone **10**. The intrinsic reversibility of the [4+2]-cycloaddition reaction reveals that these tricyclodecadienones are *synthetic equivalents* of cyclopentadienones in which one of the double bonds is masked. Chemical transformations in the tricyclic system, for example, by nucleophilic additions to the remaining enone moiety followed by electrophilic substitutions to give **13** and a subsequent retro Diels−Alder reaction regenerates the enone function to produce functionalized cyclopentenones **11**. This synthetic strategy not only offers a unique solution to the problem of the intrinsic instability of cyclopentadienones by temporally protecting one of the double bonds but such a protection simultaneously transforms the nonchiral flat cyclopentadienone molecule into a chiral rigid structure with a pronounced difference in stereoheterotopic faces, thereby fulfilling the conditions for attaining an acceptable degree of stereoselectivity, for example, in addition reactions at the enone moiety. Removal of the protecting ring system, e.g., cyclopentadiene, not only leads to recovery of the original double bond but also eliminates the stereogenic element that initiated the stereoselective generation of subsequent

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Antonius J. H. Klunder was born in 1945 in Enschede, The Netherlands. He received his M.Sc. degree from the University of Groningen in 1968 on a synthetic study of five-membered heterocycles annealated to bicyclic systems in the laboratory of Professor H. Wijnberg. He moved to Nijmegen, where he earned the Ph.D. degree from the University of Nijmegen in 1973 on research undertaken with Professor B. Zwanenburg on the synthesis and properties of highly strained cage compounds such as the cubane and homocubane systems. In 1975, he did postdoctoral work on the rearrangement of [4.3]spirooctadienes with Dr. R. D. Miller at the IBM Research Center at San Jose, CA. He returned to Nijmegen, where he joined the group of Professor B. Zwanenburg. He was appointed lecturer in 1975 and to "Universitair Hoofddocent" (Associate Professor) in 1984. His main research interest is currently directed on the utilization of polycyclic structures for the synthesis of interesting natural and unnatural compounds. Enzymes, gas-phase thermolysis, and heterogeneous catalysis play an important role therein. He is author of more than 110 papers and chapters.

Jie Zhu was born in 1956 in Shanghai, China. After his study at the Shanghai Hygienic School, he received his chemical education at the Shanghai Institute of Organic Chemistry (Chinese Academy of Sciences) where he was involved in the total synthesis of the natural product Arteannuim and analogues in the group of Professor Wei-Shan Zhou. He continued his study at the Shanghai Second Polytechnic University and then returned to the Shanghai Institute of Organic Chemistry. In 1991 he joined the group of Professor Zwanenbug and Dr. Klunder at the University of Nijmegen, The Netherlands, where he received his Ph.D. degree from the University of Nijmegen in 1995 on research on the exploration of the *endo*-tricyclo[5.2.1.$0^{2,6}$]decadienone system for the synthesis of natural products. In 1995, he started postdoctoral work in an industrial project with Professor B. Zwanenburg, concerning the semisynthesis of β-lactam antibiotics. His research interests include the asymmetric synthesis of α-aminoacid, the use of enzymes in organic synthesis, and solid-state organic synthesis.

Binne Zwanenburg was born in 1934 in Lippenhuizen, The Netherlands. He received his M.Sc. and Ph.D. degree from the University of Groningen, The Netherlands, in 1959 and 1962, respectively, on a kinetic study of acetylenic ethers under the supervision of Professors J. F. Arens and W. Drenth. He did postdoctoral work with Professor R. A. Raphael at the University of Glasgow, Scotland, on the Favorskii rearrangement (1963) and with Professor N. J. Leonard at the University of Illinois, Urbana-Champaign, IL, on azirine chemistry (1964–1965). He joined the research group of Professor Strating in 1961 and studied the synthesis of sulfines and the mechanism of reactions of diazo sulfones. He was appointed Assistant Professor at the University of Groningen in 1963 and Associate Professor in 1965. During the period from 1965–1971 he continued with his investigations into sulfine chemistry and also began studies on the chemistry of strained cage compounds and functionalized small-ring systems. These have remained an abiding interest. He was also responsible for the planning of the building of a new chemical laboratory in Groningen in this time. He accepted his present position as Professor of Organic Chemistry at the University of Nijmegen in 1971. He was appointed adjunct Professor at Bowling Green State University in 1980 and has been a Visiting Professor at Dalhousie University, Halifax (Nova Scotia), the Science University of Tokyo, and the University of Bologna. He has been an active, serving member of many boards and committees, both national and international, during his career. These include Chairmanship (1985–1991) of the Netherlands Foundation for Chemical Research (SON), Chairmanship (1993–1996) of the National Foresight Committee in Chemistry, Dean of the sub-Faculty of Chemistry (1977–1980; 1991–1995) and Vice Chairman of the Faculty of Science (1995–1998) of the University of Nijmegen; member of International Advisory Board International Conferences on Heteroatom Chemistry (1989 to date) and Symposia on the Organic Chemistry of Sulfur (1986 to date); Chairman of NATO panel Advanced Study Institutes/Advanced Research Workshop Program (1992–1994); member fo the Evaluation Committee for Chemistry at Universities of Flanders (Belgium), (1923) and Universities of Lower Saxony (Germany) (1996); and member (1998) of the International Review Committe Interuniversity Consortium Chemistry for the Environment (INCA), Italy; coordinator of the Erasmus project between Universities of Nijmegen, Bologna, and Camerino (1988 to present); coordinator of the cooperation project University of Dar es Salaam (Tanzania) and University of Nijmegen (1978 to present). His research interests include organic sulfur chemistry (sulfines), functionalized small-ring heterocycles (epoxides and aziridines), strained polycyclic systems (cubane-type structures), design, and synthesis of herbicides (germination stimulants); synthetic methodology; asymmetric synthesis; synthesis of natural products; organic enzyme chemistry; flash vacuum thermolysis (FVT); utilization of clay minerals as catalysts in organic synthesis. His scientific work has been reported in over 350 papers and reviews.

stereogenic centers. Hence, the protection and deprotection sequence shown in Scheme 1 involves the transfer from achirality to chirality and back to achirality when the masked enone moiety is taken as the reference. For such a process, the term *transient chirality* may be appropriate. It is evident that the success of the strategy depicted in Scheme 1 is dependent on the degree of stereocontrol imposed by the tricyclic skeleton and also on the conservation of stereochemistry during the thermal cycloreversion reaction. Finally, the availability of appropriately functionalized tricyclodecadienones in enantiomerically pure form is of crucial importance. In recent years, we and others have proven the merit of this

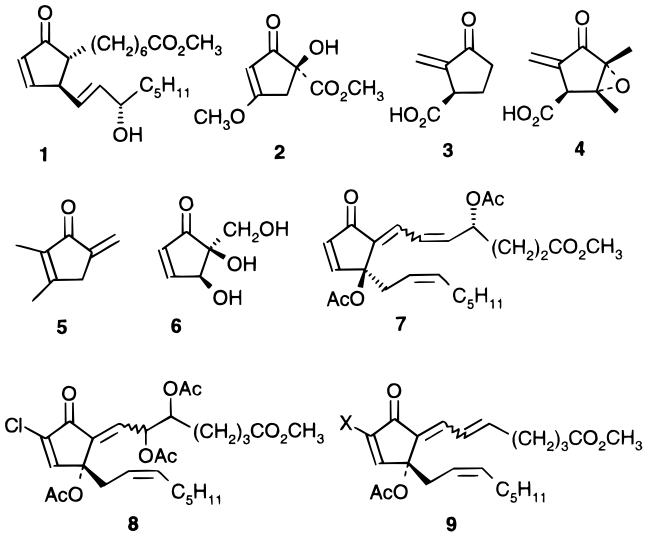
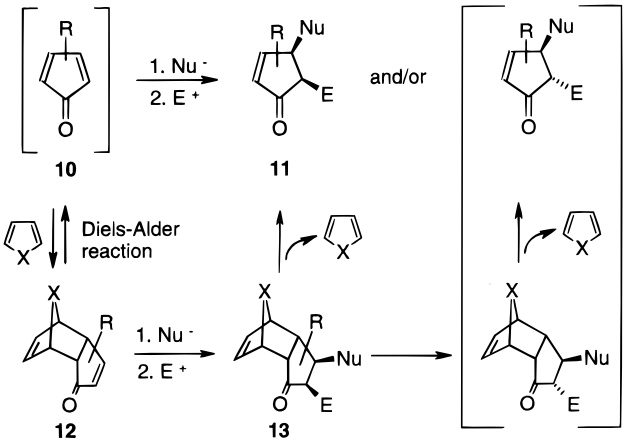


Figure 1.

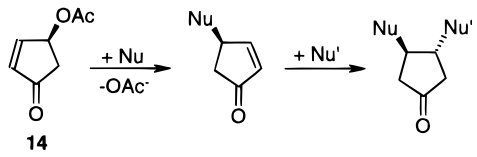
Scheme 1



synthetic methodology for the stereoselective synthesis of a great variety of naturally occurring cyclopentanoids and pharmacologically important structures.

It is clear that this concept of *transient chirality* is not restricted to the tricyclodecadienone system **12** but can easily be extended to other cyclic systems applying other dienes and dienophiles. It is even not restricted to the Diels−Alder/retro-Diels−Alder approach. A striking example of *transient chirality* is also found in the elegant work of Winterfeldt who uses γ-acetoxycyclopentenone **14** as the synthetic equivalent of cyclopentadienone applying the strategy depicted in Scheme 2.[2] In this review, attention will be primarily focused on the concept of *transient chirality* applying the Diels−Alder/retro-Diels−Alder methodology.[3]

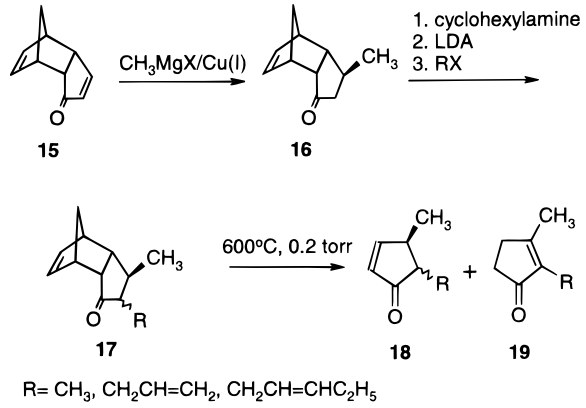
Scheme 2



II. Cyclopentanoids

The earliest example of the stereoselective synthesis of cyclopentanoids which meets the criteria given above was published in 1971 by the group of Stork[4] applying the parent *endo*-tricyclodecadienone **15** for the synthesis of vicinal dialkylated methylcyclopentenones **18** (Scheme 3). The first step in this route

Scheme 3

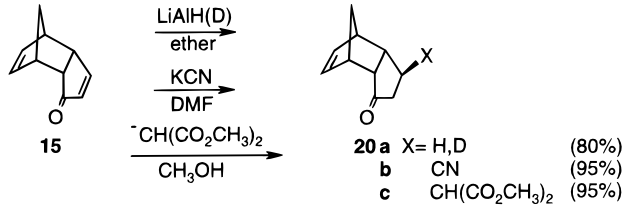


involves the Cu(I)-catalyzed addition of methylmagnesium halides to **15**, which (as shown three years earlier by Sakan)[5] is completely stereoselective and occurs with exclusive addition to the *exo*-face of the tricyclic system to give **16**. Interception of the intermediate enolate with reactive halides (allyl bromide, methyl iodide) yielded *trans*-vicinal α-alkyl-β-methyltricyclic ketones **17** together with appreciable amounts of geminal α,α-dialkylated product. Prevention of the unwanted dialkylation was achieved by using the metalloenamine procedure which was developed a few years earlier by Stork.[6] Using *cis*-1-chloro-2-pentane as the alkylating reagent and the cyclohexylimine of β-methyl-substituted **16**, a mixture of 53% *cis*-**17** and 47% *trans*-**17** was thus obtained. Although not firmly proven, it was assumed that alkylation of the intermediate enamine of **16** occurs again preferentially from the *exo*-face and that the kinetic product may well be exclusively the *cis*-α,β-disubstituted ketone **17**. The formation of *trans*-**17** is then explained by partial epimerization of the *cis*-isomer. Equilibration with 10% ethanolic potassium hydroxide transformed the mixture into pure *trans*-isomer **17**. Completion of the cyclopentenone synthesis required a detailed study of the optimum conditions for the thermal cycloreversion of tricyclodecenones. Both thermolysis under atmospheric pressure or heating in a sealed tube were not satisfactory as migration of the double bond in the initially produced cyclopentenones occurred and mixtures of **18** and **19** were obtained. Pure cyclopentenones **18** were eventually obtained in quantitative yield by slow addition of tricyclodecenones **17** at the top of a quartz column filled with quartz chips and maintained at 600 °C under 0.2 mm pressure. This early observation that the stereochemistry present in the original adducts **17** was completely retained in the cyclopentenones **18**, despite the high temperatures used for the cycloreversion, shows that the general strategy depicted in Scheme 1 is not complicated by loss of the stereochemical integrity during the thermal generation of the olefinic bond.

The complete *exo*-stereoselectivity observed for the Cu(I)-catalyzed 1,4-addition of Grignard reagents to

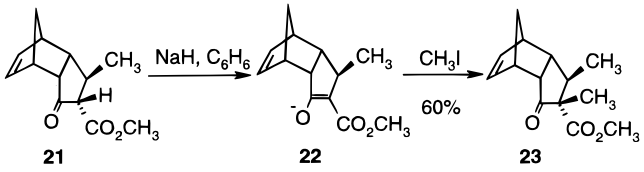
15 appeared to be quite general.[7] The 1,4-reduction using lithium tri-*tert*-butoxyaluminum hydride and the additions of nitrile using potassium cyanide and diethyl malonate anion all proceeded with exclusive *exo*-stereochemistry and in high yields to give β-substituted tricyclodecenones **20** (Scheme 4). These

Scheme 4



results prove that the *endo*-face of the parent tricyclodecadienone system is much less accessible than the *exo*-face due to a more effective steric shielding by the C_8-C_9 ethylene bridge as compared with the C_{10} methylene bridge. Interestingly, the presence of an *exo*-methyl group at the C_β position does not effect the preference for *exo*-addition, as demonstrated by the α-methylation of β-methyltricyclodecenone ester **21** using sodium hydride in benzene (Scheme 5).

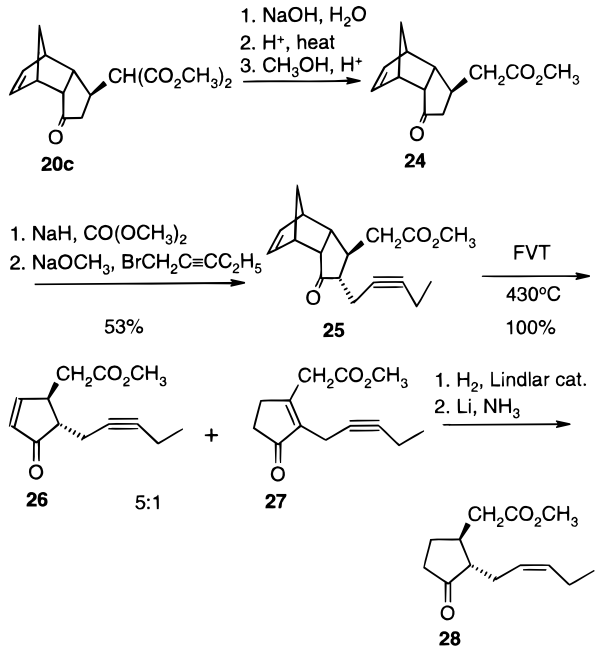
Scheme 5



Assuming the initial formation of enolate **22**, *exo*-α-methyl ester **23** was obtained as the exclusive product in 60% yield.[7]

The malonate addition product **20c** was applied for the synthesis of *rac*-jasmonate **28** (Scheme 6).[8] Sa-

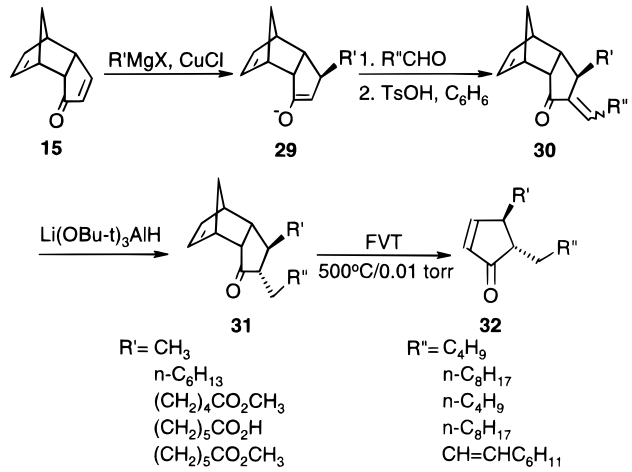
Scheme 6



ponification followed by decarboxylation produced ester **24** in 50% yield. Condensation with dimethyl carbonate followed by alkylation with 1-bromopent-2-yne and decarboxymethylation gave *trans*-**25** in 53% overall yield. Thermolysis of **25**, applying gas flow thermolysis at 430 °C in a quartz tube, gave a 5:1 mixture of cyclopentenones **26** and **27** in quantitative yield. Selective hydrogenation of the alkyne moiety to the *cis*-alkene using a Lindlar catalyst followed by reduction of the enone with lithium in ammonia afforded the desired jasmonate **28**. This route to jasmonate is in fact the first example of the synthesis of a natural cyclopentenoid based on the strategy depicted in Scheme 1.

The strategy depicted in Scheme 3 was successfully applied for the synthesis of a wide variety of *trans*-α,β-disubstituted cyclopentenones **32**, including prostaglandins PGA_2 derivatives (Scheme 7).[9,10] Instead

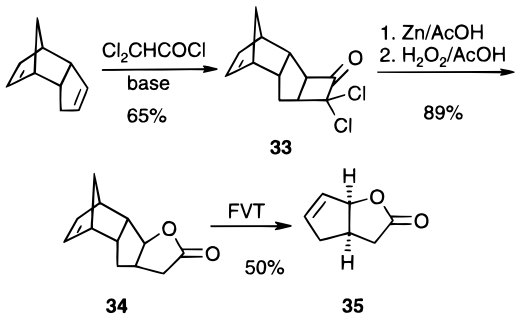
Scheme 7



of using alkyl halides for the introduction of the α-substituent, condensation of enolate **29**, formed by the 1,4-addition of the Grignard reagent, with an appropriate aldehyde, followed by dehydration to the *exo*-methylene cyclopentenones **30** and subsequent 1,4-hydride reduction was applied in order to avoid polyalkylation. Gas-phase pyrolysis of the thus obtained *trans*-dialkylated tricyclodecenones **31** at 500 °C and 0.01 Torr led to complete cycloreversion to give the expected *trans*-2,3-dialkylated cyclopentenones **32** in quantitative yield, without any double-bond isomerization. This observation that gas-phase pyrolysis under reduced pressure did not lead to isomerization of **31** has been crucial for the further development of the synthetic methodology depicted in Scheme 1. This thermolysis technique, which is better know as *flash vacuum thermolysis (FVT)* or *pyrolysis (FVP)*,[11] is characterized by very short reaction or contact times which generally prevent the occurrence of secondary reactions and allow the synthesis of kinetically unstable compounds. The products are trapped at low temperatures (−78 to −190 °C) immediately after they leave the hot zone, which is usually a quartz tube heated by an oven.

An interesting and effective stereoselective approach to annulated cyclopentenes involves the cycloaddition of *endo*-dicyclopentadiene with dichloroketene (Scheme 8).[10] A mixture of two regioisomeric

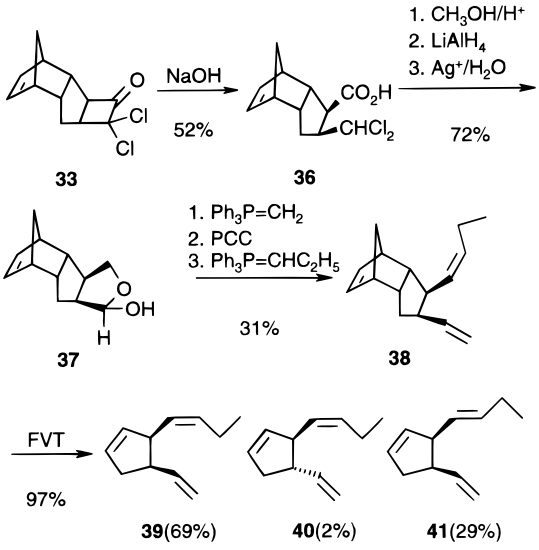
Scheme 8



cycloadducts was obtained with **33** predominating. Addition occurred only at the *exo*-face of the annulated cyclopentene moiety. Reduction with zinc in acetic acid to remove the chlorine substituents, followed by Baeyer−Villiger oxidation with hydrogen peroxide in acetic acid, gave lactone **34**. Cycloreversion at 600 °C and 0.04 Torr gave bicyclic lactone **35** in 50% overall yield from dicyclopentadiene.

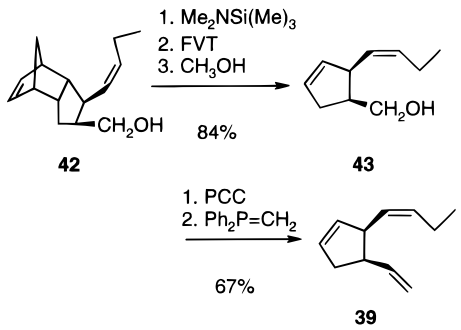
The [2+2]-cycloaddition of dichloroketene and *endo*-dicyclopentadiene also constituted the starting reaction for the synthesis of *rac*-multifidene and related structures (Scheme 9).[12] Multifidene (**39**), a highly

Scheme 9



unsaturated cyclopentene derivative with a *cis*-vicinal substitution pattern, is the major constituent of the essential oil of the Mediterranean seaweed *Cutleria multifida* which functions as a chemical signal in the control of the reproduction. Dicyclopentadiene was selected as the starting compound as it allows vicinal *cis*-substitution by initial ketene cycloaddition and already contains, although masked, the cyclopentene double bond. Dichloroketene addition product **33** was ring opened with sodium hydroxide in water/dioxane to give a mixture of carboxylic acids which could be separated by crystallization to give **36** as the major product in 52% yield (Scheme 9). Hydride reduction followed by silver-catalyzed hydrolysis of the dichloromethyl group led to lactol **37**, which was subjected to a Wittig reaction to introduce the vinyl side chain, then oxidized to the *cis*-vinyl aldehyde, and again reacted in a Wittig reaction with triphenylpropylidene phosphorane to give the desired *cis*-disubstituted tricyclodecene **38**. Flash vacuum thermolysis of **38** at 500 °C and 1 Torr using a small gas flow of argon led to complete cycloreversion which, however, was accompanied by substantial rearrangement of the initially formed multifidene **39**. Under the thermal conditions applied, **39** undergoes a double Cope rearrangement to give considerable quantities of stereoisomers **40** and **41**. Lowering the pyrolysis temperature did increase the relative yield of **39**; however, the cycloreversion was then far from complete. To avoid this undesired [3+3]-rearrangement, an alternative sequence was chosen, viz. introduction of the vinyl group after the thermal generation of the cyclopentene system (Scheme 10).[13]

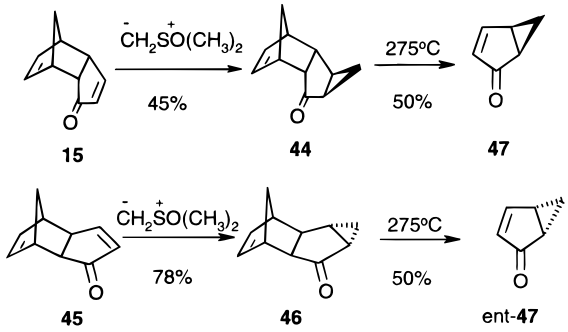
Scheme 10



It turned out that neither the free alcohol due to its low volatility nor the corresponding aldehyde or ester gave satisfactory results. Considerable amounts of *trans*-substituted disubstituted cyclopentenes were obtained, most likely due to the intermediate formation of biradicals or enolization of the carbonyl moiety. An elegant solution to the problem appeared to be the use of the corresponding trimethylsilyl ether of **42**. Flash pyrolysis at 500 °C and 1 Torr applying an argon flow now proceeded smoothly to give, after removal of the silyl group, cyclopentene **43** in an excellent yield with only minor amounts of *trans*-impurities present. Subsequent oxidation and Wittig olefination afforded multifidene **39** in an acceptable overall yield with high stereochemical purity. This sequence of reactions has also been used for the synthesis of a series of congeners of multifidene.

The cyclopropanation of *endo*-tricyclodecenone **15** applying dimethyloxosulfonium methylide was also found to be completely stereoselective, affording only *exo*-annulated tetracyclo[6.2.0.^{2,7}0^{4,6}]undecenone **44** (Scheme 11).[14] Interestingly, it was shown here for

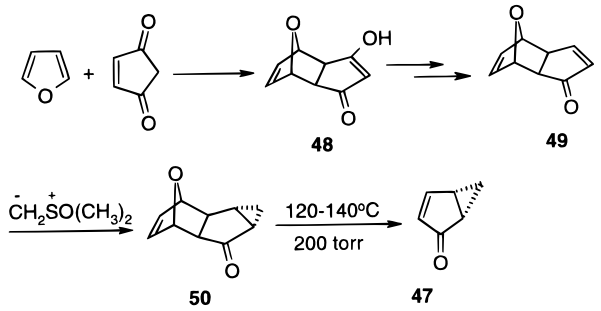
Scheme 11



the first time that additions to the enone moiety in the *exo*-tricyclodecadienone system **45** give similar high stereoselectivities as those observed for the *endo*-system **15**. The observed stereochemistry of product **46** is not surprising as the *exo*-face of the cyclopentenone moiety in **45** is clearly more accessible than its *endo*-face. The cycloreversion of both **44** and **46** was accomplished by static thermolysis in mineral oil at 275 °C. In this way, the interesting bicyclo-[3.1.0]hex-3-en-2-one (**47**) was obtained in 50% yield. It should be noted that the absolute chemistry of the cyclopentenones **47** obtained from *endo*-**44** and *exo*-**46** is opposite. Since the applied tricyclodecenones are racemic, this structural aspect has no meaning here. Recently, an enantiomerically pure bicyclo-[3.1.0]hexane derivative was prepared essentially along the same route starting from enantiomerically pure tricyclodecadienone **15** *(vide infra).*[15]

A similar approach, but now based on the *exo*-7-oxatricyclodecadienone system **49** which is readily prepared from the Diels−Alder adduct of furan and cyclopentene-1,4-dione **48**, was reported one year earlier by Oda et al. (Scheme 12).[16] Again, cyclopro-

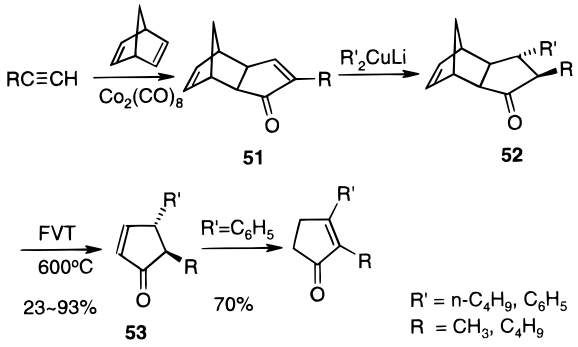
Scheme 12



panation of **49** appeared completely stereoselective to afford **50**. Flow pyrolysis of **50** at temperatures as low as 120−140 °C at 200 Torr produced **47** in 64% yield from **49**. The relative low temperatures required for the cycloreversion of **50** is the consequence of the aromaticity of the liberated furan.

So far, most approaches to substituted cyclopentenones, according to the synthetic strategy outlined in Scheme 1, were based on the *endo*-tricyclodecadienone system as this tricyclic system, at that time, was readily available by a two-step oxidation of the cyclopentadiene dimer which predominantly has the *endo*-configuration.[17,18] Its *exo*-isomer was only obtainable after laborious separation procedures and in relatively small quantities. The elegant and, as it turned out later, widely applicable co-cyclization of acetylenes with norbornadiene and carbon monoxide, discovered by Pauson and Khand, changed this picture and made the *exo*-tricyclo[5.2.1.$0^{2,6}$] decadienone system more readily available.[19] Realizing possible advantages of the *exo*-tricyclodecadienone system for the stereoselective synthesis of substituted cyclopentenones, Schore studied the cuprate additions to 4-substituted *exo*-tricyclodecadienones **51** (Scheme 13).[20] Again, complete stereoselectivity was observed to give *trans*-4,5-dialkylated tricyclodecenones **52** in excellent yields. Thermolysis of **52** was effected by FVT at 600 °C applying a quartz tube

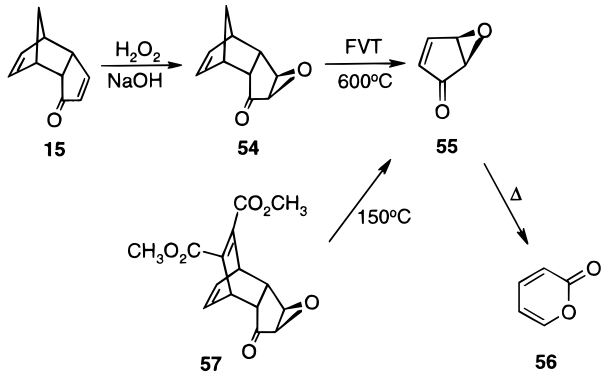
Scheme 13



filled with quartz chips to produce *trans*-2,3-dialkylated cyclopentenones **53**. In the case of R′ = Ph, considerable double-bond isomerization was observed.

In 1979 Chapman and Hess published an interesting study on the preparation of cyclopentadienone epoxide **55**, a hitherto unknown derivative of cyclopentadienone (**10**, R = H), although postulated as an intermediate in the photochemical transformation of 4-pyrones to 2-pyrones.[21] Their initial attempts were based on the cycloreversion strategy and started from parent tricyclodecadienone **15**. Alkaline epoxidation using hydrogen peroxide in the presence of sodium hydroxide afforded the *exo*-epoxide **54** as the exclusive product in almost quantitative yield, showing again that *endo*-addition to the enone moiety in **15** is unfavorable (Scheme 14). Unfortunately, their

Scheme 14



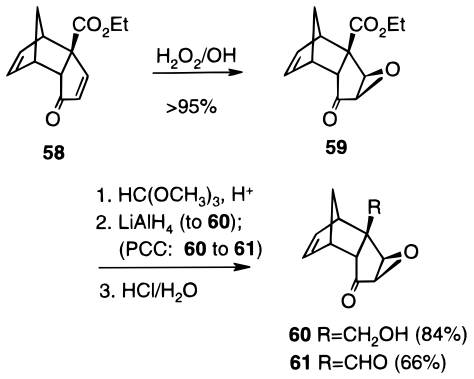
attempts to produce the desired cyclopentadienone epoxide **55** by FVT at 600 °C and 0.01 Torr were not successful as at this temperature a fast and efficient [$4\pi_a + 2\pi_a$] cycloreversion of the initially formed **55** takes place to form 2-pyrone **56**. By taking the tricyclic epoxide **57**, which on cycloreversion would yield an aromatic compound viz. dimethyl phthalate, the temperature needed for the retro-Diels−Alder reaction dropped to 150 °C, which was sufficiently low to prevent the isomerization to the 2-pyrone and **55** was isolated in 98% yield.

Although the aforementioned pioneering work of the research groups of Rouessac and Boland already indicated the synthetic potential of the tricyclodecadiene system as a synthetic building block for cyclopentanoid natural products, its synthetic merit was recognized after the successful stereoselective syntheses of the naturally occurring antibiotics terrein

and pentenomycin. Inspired by the attempts of Chapman and Hess to prepare cyclopentadienone epoxide **55** by flash vacuum thermolysis of tricyclodecadienone epoxide **54** (Scheme 14), we considered both epoxides as interesting synthons for highly oxygenated cyclopentenoids. Although the results of Chapman and Hess were not particularly encouraging, it was reasoned that appropriate functionalization could considerably increase the thermal stability of the cyclopentadienone epoxide system, thus making the subsequent thermal rearrangement less favorable.

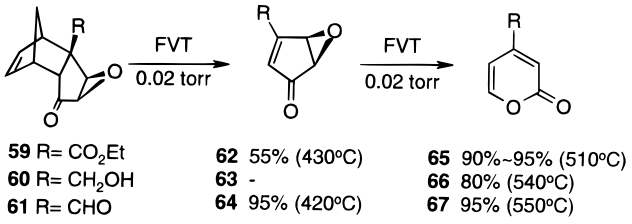
A practical synthesis of 6-functionalized cyclopentadienone epoxides and their dimethyl acetals was accomplished starting from ethyl tricyclodecadienone 3-carboxylate **58**, which is readily accessible from benzoquinone and cyclopentadiene (Scheme 15).[22,23]

Scheme 15



Alkaline epoxidation of **58** with hydrogen peroxide occurred exclusively from the sterically less hindered convex face of the tricyclodecadienone skeleton to give *exo*-epoxide ester **59** in quantitative yield. The complete stereoselectivity observed in this nucleophilic epoxidation of the enone moiety shows that the γ-ester function does not affect the accessibility of the *exo*-face of the enone in such a way that *endo*-addition would be competitive. To achieve selective conversion of the ester function, the cyclopentanone carbonyl group was protected as the dimethyl acetal. Hydride reduction and subsequent oxidation with pyridinium chlorochromate, followed by deprotection of the ketone function with aqueous hydrogen chloride, led to tricyclic alcohol **60** and aldehyde **61**, respectively, in excellent overall yields. All three tricyclic epoxy ketones **59**, **60** and **61** were subjected to flash vacuum thermolysis (Scheme 16). At ca. 500 °C and 0.02 Torr,

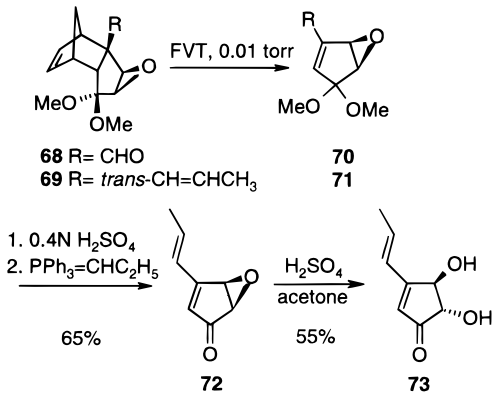
Scheme 16



almost complete cycloreversion was observed for all epoxy ketones. At that temperature both ester **59** and aldehyde **61** produced mixtures of cyclopentadienone epoxides and α-pyrones, **62** and **65** and **64** and **67**, respectively. Optimum yields for cyclopentadienone epoxides **62** and **64** were obtained at 430 and 420 °C, respectively. Only in case of aldehyde **61** could the pyrolysis be controlled in such a way that epoxide **64** was obtained as the exclusive product. Thermal reaction of alcohol **60** did not lead to any cyclopentadienone epoxide **63**. At 400−450 °C, only starting alcohol and α-pyrone **66** were obtained. When pyrolysis temperatures over 500 °C were applied, complete and almost quantitative conversion into the corresponding α-pyrones was observed in all three cases. These results convincingly demonstrate that the thermal stability of cyclopentadienone epoxides is considerably enhanced by extending the conjugation of the cycloenone system. As a consequence, cyclopentadienone epoxides such as **62** and **64** can be efficiently generated by gas-phase pyrolysis of appropriate tricyclodecenones. When such an extended π-system is lacking, the cyclopentadienone epoxides rapidly rearrange to the corresponding α-pyrones under the conditions of the thermal fragmentation. For preparative purposes, this cycloreversion constitutes a useful route to functionalized cyclopentadienone epoxides and α-pyrones. Both classes of compounds are important structural entities in natural product synthesis. The high-yield generation of epoxy aldehyde **64** is a mere demonstration of the great potential of the flash vacuum thermolysis technique. By choosing short reaction times (oven length only 16 cm and unpacked) and carefully selecting the pyrolysis temperature, formation of α-pyrone **67** could be completely avoided. It should be noted that a relatively small increase in temperature causes a subsequent rearrangement of the initially formed cyclopentadienone epoxides to the corresponding α-pyrones. These strained highly functionalized five-membered ring compounds are not attainable at all, applying the conventional wet chemistry as they rapidly react with both nucleophilic and electrophilic reagents. The many attempts to isolate or synthesize cyclopentadienone epoxides in solution have always been in vain.[24]

The first example of the synthetic applicability of cyclopentadienone epoxides in natural product chemistry is the stereoselective synthesis of *rac*-terrein **73**, a mold metabolite from *Aspergillus terreus*.[25] Although already isolated in 1935, its sensitivity to acid and base precluded an efficient synthesis. Tricyclic aldehyde **68** was the starting material of choice (Scheme 17). In the same efficient manner as that described for aldehyde ketone **64**, flash vacuum thermolysis (475 °C, 0.1 Torr) of **68** led to a quantitative formation of **70**. Subsequent Wittig-ethenylidation afforded the *trans*-propenyl derivative **72** in 55% yield. This compound can also be prepared by ethenylidation of tricyclic aldehyde **68** to give alkene **69**, which was followed by thermolysis (450 °C, 0.1 Torr) to yield **71**. However, this sequence of steps is less efficient as **71** is now obtained in only 35% yield, after a tedious column chromatographic separation step. Selective hydrolysis of the dimethyl ketal function of **71** was accomplished with 0.4 N sulfuric acid in

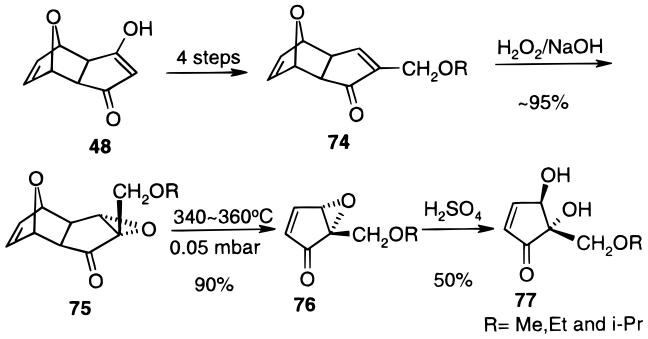
Scheme 17



ether at room temperature to give cyclopentadienone epoxide **72** in 65% yield. Using 1% of an aqueous 5 N sulfuric acid solution in acetone led, after 4 days of stirring at room temperature, to *rac*-terrein **73** in 55% yield.

Having successfully completed the terrein synthesis, a route to *epi*-pentenomycin, also containing a vicinal *trans*-diol moiety, was devised. Applying the same strategy, it proved necessary to use 10-oxatricyclodecadienone **74** as the starting tricyclic enone (Scheme 18). These furan-derived Diels−Alder ad-

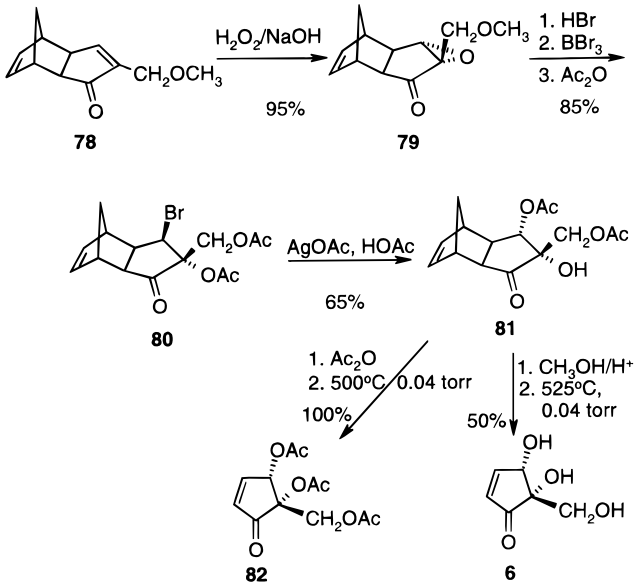
Scheme 18



ducts undergo cycloreversion at such a temperature that no competitive rearrangement of the initially formed cyclopentadienone epoxides to α-pyrones takes place.[26−28] Starting from tricyclic enol **48**, a series of 3-alkoxy methyloxatricyclodecadienones **74** was synthesized (Scheme 18).[26,28] Alkaline epoxidation of **74** led stereoselectively and quantitatively to tricyclic epoxides **75**, which on flash vacuum thermolysis at temperatures as low as 350 °C (0.05 mbar) afforded the cyclopentadienone epoxides **76** in yields of 90%. Only traces of α-pyrones were detected. Subsequent hydrolysis of **76** with 1% 5 N sulfuric acid in acetone led to a smooth cleavage of the epoxide ring, affording the alkyl-protected *epi*-pentenomycins **77** in 50−60% yields.

The synthesis of *rac*-pentenomycin **6**, an antibiotic isolated from *Streptomyces eurythermus*, required a somewhat different strategy as it contains, in contrast to *epi*-pentenomycin, a vicinal diol moiety with the *cis*-configuration. Since simple hydrolysis of cyclopentadienone epoxide would lead to a *trans*-diol, *cis*-hydroxylation of an appropriately substituted tricyclodecadienone, viz. hydroxy-protected 4-hydroxymethyl-*exo*-tricyclodecadienone **78**, was considered (Scheme 19).[29] It is obvious that direct *cis*-

Scheme 19

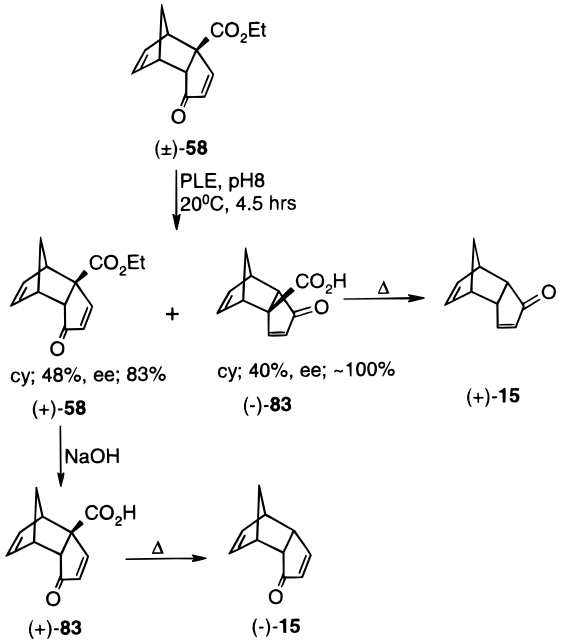


hydroxylation using electrophilic reagents is doomed to fail as the strained norbornene double bond would react preferentially. Therefore, a multistep sequence starting from *exo*-epoxide **79** was devised. Alkaline epoxidation of **78** gave stereoselectively the desired epoxide **79**, which on treatment with concentrated hydrobromic acid in methanol was regioselectively converted into a *trans*-bromohydrin in 60−80% yield. Demethylation with boron tribromide followed by acylation afforded diacetate **80** in excellent yield. Silver-assisted displacement of the bromine by an acetate group gave acetoxy alcohol **81** with the desired *cis*-configuration. Acid-catalyzed methanolysis of **81** led quantitatively to the corresponding triol, which on flash vacuum thermolysis at 525 °C and 0.04 Torr was smoothly transformed into *rac*-pentenomycin **6** in 50% yield. The relative low yield obtained in this thermolysis is mainly due to the low volatility of the triol, which requires higher preheating temperatures and consequently leads to partial decomposition of the starting triol. This effect of poor volatility is nicely demonstrated during the flash vacuum thermolysis of the corresponding tricyclic triacetate. Being much more volatile, a lower preheating temperature was needed, resulting in a quantitative formation of pentenomycin triacetate **82**.

The success of the tricyclo[5.2.1.$0^{2,6}$]dienone system as a synthon for cyclopentanoids urged us and others to find efficient routes to optically pure tricyclodecadienones and preferably to both enantiomers. Already in 1959, Woodward and Katz[17] reported a rather effective optical resolution of *endo*-tricyclodecadien-*exo*-3-ol (**84**) using 3-β-acetoxy- Δ^5-ethiocholenyl chloride as the resolving agent. Hydrolysis of the (−)-cholenyl ester followed by oxidation yielded (−)-tricyclodecadienone **15** in an acceptable overall yield and with good optical purity. Attempts to obtain the other antipode were not reported. While exploring the synthetic potential of tricyclic ester **58** for the syn-

thesis of cyclopentanoids, we realized that this ester was an ideal candidate for optical resolution. Two approaches were considered, viz. (a) the classical separation of an appropriate diastereomeric mixture and (b) enzymatic kinetic resolution. Although a classical resolution of the corresponding acid appeared possible with ephedrine as the resolving base, the efficiency (28% yield) of resolution was too low to be practical.[30] No attempts were made to improve the efficiency as the enzymatic approach turned out to be superior. Although kinetic resolution of racemic substrates using enzymes was still at its infancy in the early 1980's, we realized the potential of this novel synthetic methodology and studied the enzymatic hydrolysis of tricyclic ester **58** using pig's liver esterase (PLE). Much to our delight, PLE showed a very high enantioselectivity toward this relatively bulky ester with complete hydrolysis of the (−)-antipode of **58** within 4.5 h in a phosphate buffer at pH 8 and with 0.2 M acetonitrile as the solvent (Scheme 20).[30]

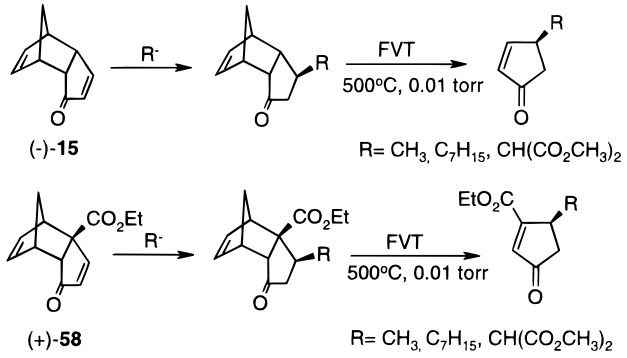
Scheme 20



The (−)-acid **83** was obtained in 40% yield at 50% conversion and with close to 100% ee. The remaining ester (+)-**58** was isolated in a yield of 48% and with 83% ee. Enantiomerically pure (+)-**58** can be obtained by repeating the enzymatic hydrolysis with this enriched ester mixture and crystallizing the residual ester from petroleum ether. Alkaline hydrolysis of this ester furnished optically pure (+)-carboxylic acid (+)-**83**. Decarboxylation of either antipode of carboxylic acid **83** was readily accomplished by heating in DMF at 100 °C to give both enantiomers of parent tricyclodecadienone **15** in optically pure form.[31] The efficiency of this enzymatic resolution is such that it can readily be carried out on a multigram scale.

The attainment of this first practical route to enantiomerically pure tricyclodecadienones now allowed the preparation of cyclopentenoids with a specific absolute configuration. To unequivocally prove that the synthetic methodology depicted in Scheme 1 did not lead to racemization in the thermal cycloreversion step, some simple γ-substituted cyclopentenones were prepared starting from enantiomerically pure tricyclodecadienone (−)-**15** and its (+)-ester **58** (Scheme 21).[32] Racemization did not occur

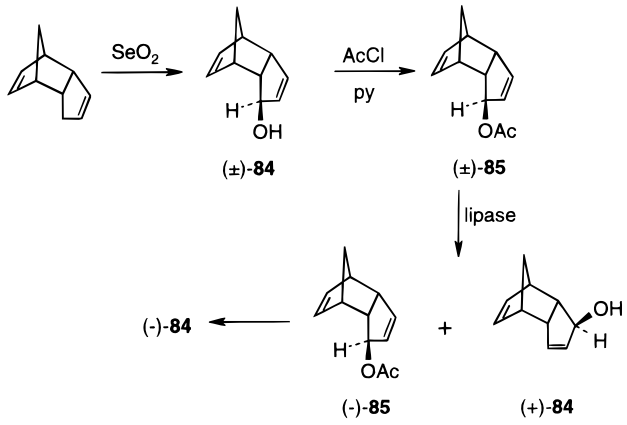
Scheme 21



in any case, and the cyclopentenones were obtained with 100% ee.

The remarkable observation that the relatively bulky tricyclodecadienyl ester **58** is an excellent substrate for enzymes triggered other groups to explore other enzymatic routes to enantiopure tricyclodecadienones. An alternative solution to this problem was developed by the group of Takano and Ogasawara starting from *endo*-dicyclopentadiene (Scheme 22).[33] Allylic oxidation using selenium di-

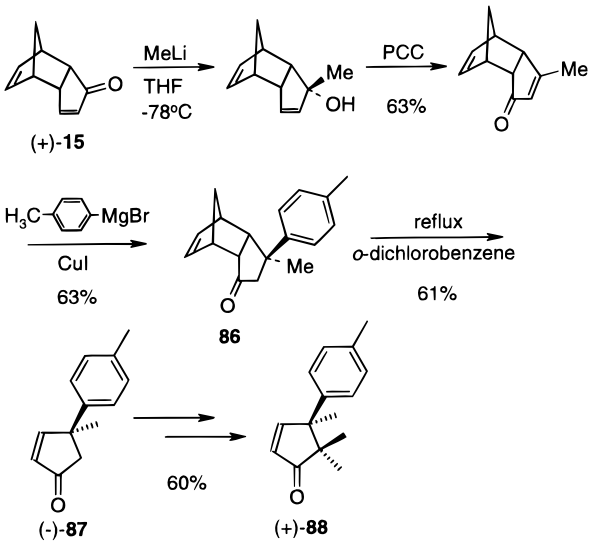
Scheme 22



oxide leads stereoselectively to the *exo*-alcohol **84**. Acetylation of **84** afforded *rac*-acetate **85**, which was subjected to kinetic enzymatic hydrolysis using *Candida cylindracea lipase* as the biocatalyst. After 5 days a mixture of (+)-alcohol **84** and the unchanged acetate **85** was obtained, which on recrystallization gave enantiopure (+)-**84** in 30% yield. The resulting acetate was hydrolyzed to the corresponding alcohol, which after recrystallization gave enantiopure (−)-**84** in 22% yield. Oxidation of these alcohols gave the corresponding optically pure tricyclodecadienones **15**.

An elegant illustration of the applicability of this approach for the enantioselective synthesis of cyclopentanoid natural products is the preparation of (+)-α-cuparenone **88** starting from (+)-tricyclodecadienone **15** (Scheme 23).[33] In this route to (+)-**88**, both the 1,2-addition of methyllithium and the 1,4-addi-

Scheme 23



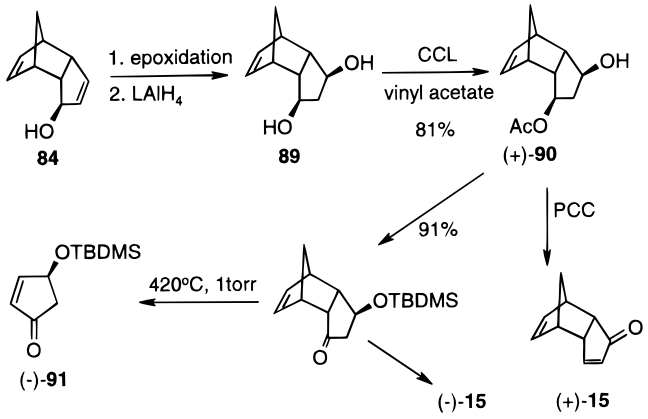
tion of *p*-tolylmagnesium bromide to the enone moiety in the respective tricyclic structures were completely stereoselective. The ultimate cycloreversion was accomplished by refluxing **86** in *o*-dichlorobenzene to give cyclopentenone (−)-**87** without racemization.

An alternative method using a transesterification approach was reported a few years later by the same group.[34] Resolution of *rac*-alcohol **84** was now achieved by employing *Pseudomonas sp Lipase* as the biocatalyst in benzene and vinyl acetate as the acyl donor affording allylic acetate (−)-**85** and unreacted alcohol (+)-**84** in good chemical and optical yields. Both antipodes **84** were eventually obtained optically pure in yields comparable with those attained in the aforementioned enzymatic hydrolysis of acetate **85** (Scheme 22).

Recently, the practical value of both methods was considerably improved by the finding that the allylic oxidation of dicyclopentadiene can be efficiently carried out with manganese triacetate instead of using selenium dioxide, which is a noxious reagent particularly when applied in large-scale preparations.[35]

So far all enzymatic routes to optically active tricyclodecadienones **15** were essentially kinetic optical resolutions which obviously suffer from the disadvantage of giving the desired antipode in 50% yield at the maximum. An elegant approach to this problem was reported by Liu et al. in the early 1990s who studied the enzymatic desymmetrization of *meso*-dihydroxytricyclodecene **89** (Scheme 24).[36] *meso*-Diol **89**, which is readily prepared by epoxidation of **84** followed by reduction with lithium aluminum hydride, was subjected to the enzymatic transesterification with vinyl acetate and *Candida cylindracea lipase (CCL)*. (+)-Acetate **90** was obtained in 81% yield in high optical purity (ee 98%). Oxidation of **90** produced (+)-tricyclodecadienone **15** in 91% yield. Conversion of (+)-**90** to the other antipode (−)-**15** was also accomplished in an acceptable overall yield using an appropriate protection/deprotection sequence. An illustration of the potential of this route is the synthesis of enantiopure (−)-4-*tert*-butyldimethylsilyloxycyclopentenone (**91**) from (+)-**90**. Very recently,

Scheme 24

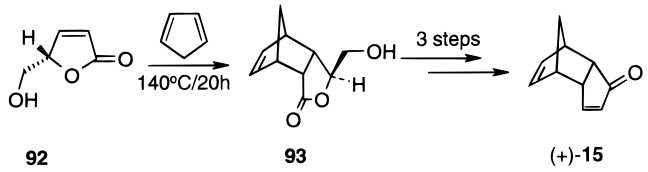


this concept of enzymatic desymmetrization was also applied by Ogasawara et al. starting from *meso*-3,5-*endo*-dihydroxytricyclodec-8-ene.[37] However, this route seems less practical.

An early example of a nonenzymatic kinetic resolution of *endo*-tricyclodecadienol **84** makes use of the Sharpless asymmetric epoxidation of allylic alcohols.[38] Recently, a second example of such a chemical kinetic resolution is reported in which the key step involves the substitution of the magnesium enolate of *racemic endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene with S_s-methyl-*p*-toluenesulfinate.[39] However, both these approaches are laborious and inefficient and certainly inferior to the enzymatic approaches.

A completely different but less practical approach to enantiopure tricyclodecadienone **15** constitutes the asymmetric Diels−Alder reaction of cyclopentadiene with (*S*)-5-hydroxymethylbutenolide **92** (Scheme 25).[40]

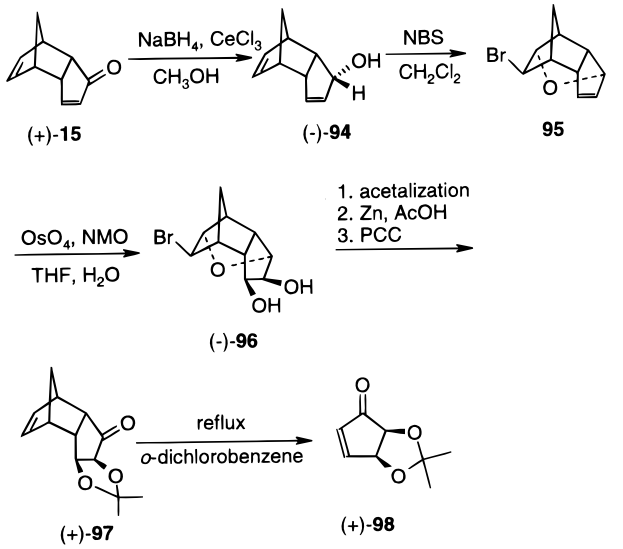
Scheme 25



The pure *endo*-adduct **93** was obtained in 72% yield by reacting both components in a sealed tube at 140 °C for 20 h. In a three-step procedure it was then converted in (+)-tricyclodecadienone **15**. This (+)-**15** was used for the enantioselective synthesis of (+)-2,3-(isopropylidenedioxy)-4-cyclopentenone (**98**) (Scheme 26). Noteworthy in this synthesis is the temporary protection of the C_8-C_9 norbornene double bond necessary to allow the *cis*-dihydroxylation at the C_4-C_5 olefinic bond. For this purpose, (+)-**15** was stereoselectively reduced to the corresponding *endo*-alcohol **94** and subsequently treated with *N*-bromosuccinimide to give tetracyclic ether **95**. Electrophilic hydroxylation applying osmium tetraoxide gave *cis*-*exo*-diol **96** with complete stereoselectivity, which after ketalization, regeneration of the C_8-C_9 double bond, and oxidation gave (+)-**97**. Cycloreversion of (+)-**97** in *o*-dichlorobenzene at reflux temperature afforded (+)-**98**.

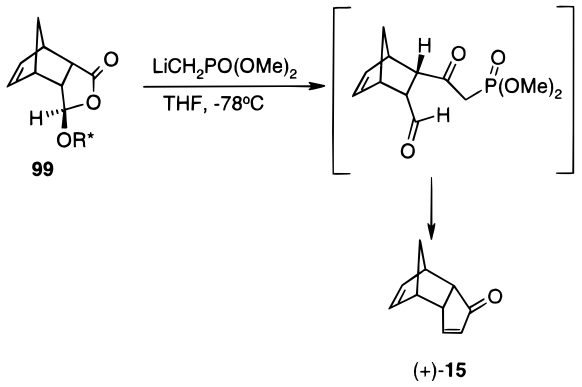
A modern and more efficient variant of this enantioselective approach to tricyclodecadienone **15** is the use of either 5-*R*- or 5-*S*−(*l*-menthyloxy)-2(5*H*)-fura-

Scheme 26



none as the dienophile to form optically pure cycloadduct **99** (Scheme 27).[41] In a one-pot procedure via

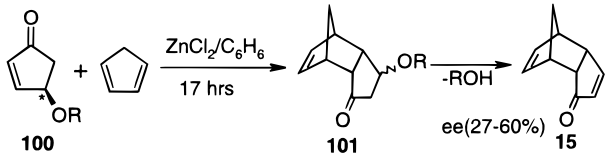
Scheme 27



ring-opening of **99** with lithium methyl dimethylphosphonate followed by intramolecular Wittig−Horner−Emmons reaction in THF, optically pure **15** is obtained in good overall yield.

The most direct and general route to enantiopure tricyclodecadienone **15** using the asymmetric Diels−Alder approach constitutes the reaction between enantiopure 4-oxycyclopentenones **100** and cyclopentadiene (Scheme 28).[42] Applying $ZnCl_2$ as the Lewis

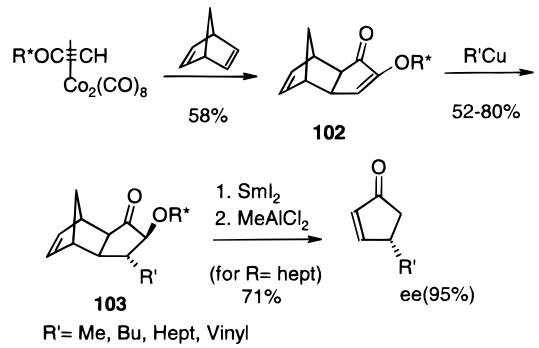
Scheme 28



acid, good yields of the *endo*-adducts **101** were formed, which on treatment with base yielded **15**. Unfortunately, due to opposing steric and electronic effects, the diastereofacial selectivity of the asymmetric cycloadditions was only moderate (27−61%) and therefore not of practical use. A practical modification was described a few years later by the group of Ogasawara, who used the $ZnCl_2$-catalyzed Diels−Alder reaction of enantiomerically pure 4-*tert*-butoxycyclopent-2-enone with cyclopentadiene as the key reaction for the synthesis of both (+)- and (−)-**15**.[43] Both the overall chemical and optical yields were now quite acceptable.

In 1994 the first example of an asymmetric intermolecular Pauson−Khand reaction was reported which allowed the synthesis of diastereomerically pure *exo*-tricyclodecadienone **102** in good yield (Scheme 29).[44] Cuprate addition to **102** led completely stereo-

Scheme 29

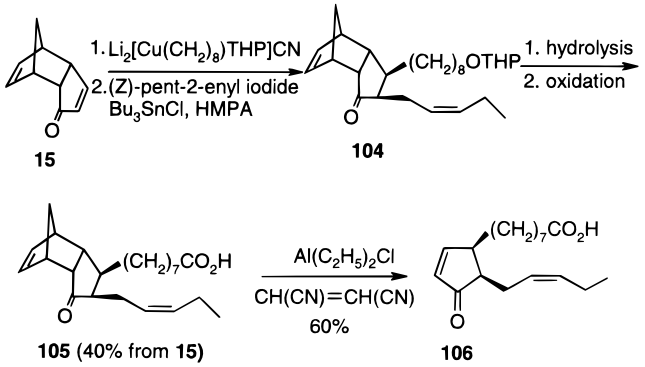


selective to the *trans*-disubstituted ketones **103**, which on reductive elimination of the chiral auxiliary, followed by Lewis acid-catalyzed cycloreversion, gave the corresponding γ-substituted cyclopentenones in good yields and with excellent optical purity. In a later report, this same procedure was used to accomplish the total synthesis of natural (+)-Brefeldin A.[45]

The availability of efficient enantioselective synthetic routes to the tricyclodecadienone system **12** together with the complete stereoselectivity generally observed for addition and substitution reactions to this tricyclic dienone opens an avenue to the enantioselective synthesis of a variety of complex natural or pharmaceutically important structures. Some of the most illustrative examples are presented below.

The total synthesis of 12-oxophytodienic acid **106** (12-oxoPDA), an extremely sensitive cyclopentenone widely distributed in plants, is a unique demonstration of the potential of the methodology depicted in Scheme 1 (Scheme 30).[46] Having a vicinal *cis*-3,4-

Scheme 30

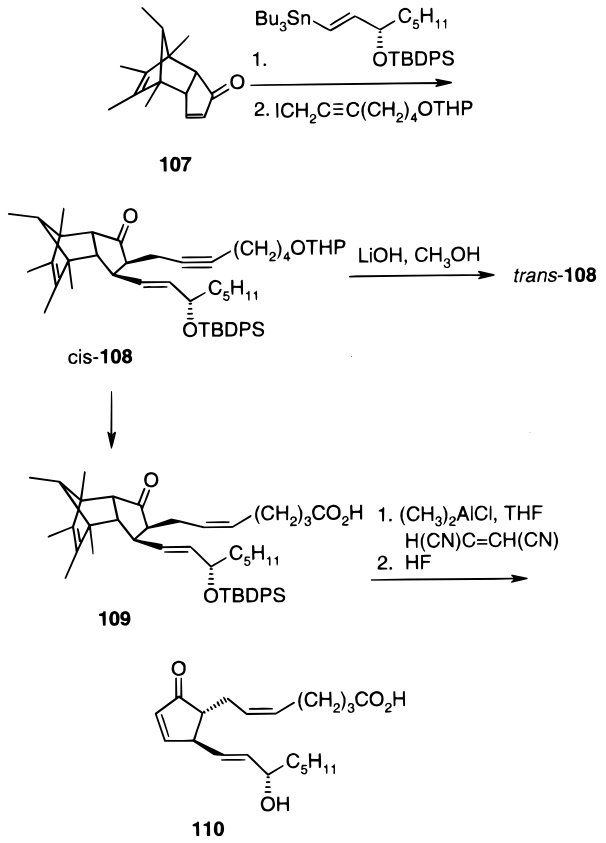


substitution pattern, these cyclopentenones are almost inaccessible owing to fast epimerization of the

C_5 substituent even under mild acidic and basic conditions, producing the thermodynamically more stable *trans*-isomer. Starting from enantiopure **15**, a three-component coupling process was employed to give **104**. Cuprate addition followed by substitution of the intermediate enolate with pentenyl iodide led exclusively to *exo-cis*-disubstituted **104** showing that, despite the steric hindrance exerted by the *exo*-substituent at C_5, *exo*-substitution at the C_4 position is still the preferred stereochemistry. Attack of the electrophile from the *endo*-face is apparently still far more unfavorable. In addition, under the reaction condition used, no epimerization at the C_4 position is observed. Mild hydrolysis and oxidation gave **105**, which on treatment with dimethylaluminum chloride in 1,2-dichloroethane in the presence of fumaronitrile gave a smooth [4+2]-cycloreversion to the desired (+)-12-oxophytodienic acid **106**. The presence of fumaronitrile as a dienophile was shown to be essential as the efficiency of this process dropped considerably in its absence. The sensitivity of **106** to epimerization was shown by brief treatment with acid, which led to rapid and complete transformation to its *trans*-isomer.

Essentially the same procedure was used for the synthesis of (+)-15(S)-prostaglandin A_2 **110** starting from (+)-pentamethyltricyclo[5.2.1.$0^{2,6}$]decenone **107** (Scheme 31).[47] Again, a three-component coupling

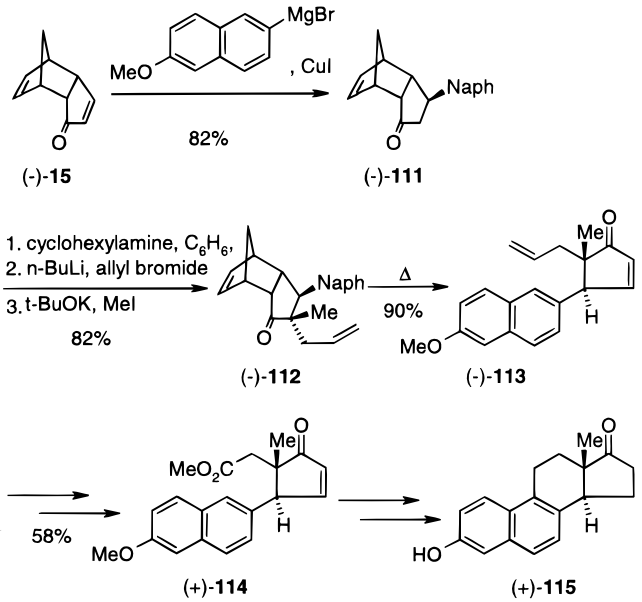
Scheme 31



process was employed to obtain **109**. Cuprate addition followed by substitution of the intermediate enolate with propargylic iodide led to *exo-cis*-disubstituted **108**. Complete isomerization to *trans*-**108** was accomplished by treatment with methanolic lithium hydroxide. *cis*-**108** was converted in **109** *via* a three-step sequence. Smooth [4+2]-cycloreversion was again accomplished by employing dimethylaluminum chloride in 1,2-dichloroethane in the presence of fumaronitrile. Interestingly, attempts to employ Lewis acids to effect a retro-Diels−Alder reaction on the nor-methyl system **13** have met with no success! Removal of the protective *tert*-butyldiphenylsilyl group afforded optically pure natural PGA_2 **110**, showing that even with such sensitive compounds as prostaglandins, the use of a relatively strong Lewis acid in the cycloreversion step does not cause any racemization or double bond migration.

A notable use of the tricyclodecadiene chiron for the synthesis of estrogenic steroids was devised by the group of Takano and Ogasawara.[48] The synthesis of (+)-equilenin **115** started from parent (−)-**15**, which was subjected to a complete stereoselective 1,4-addition with 6-methoxy-2-naphthylmagnesium bromide in the presence of CuI to give β-naphthyl ketone **111** (Scheme 32). Sequential metalloenamine forma-

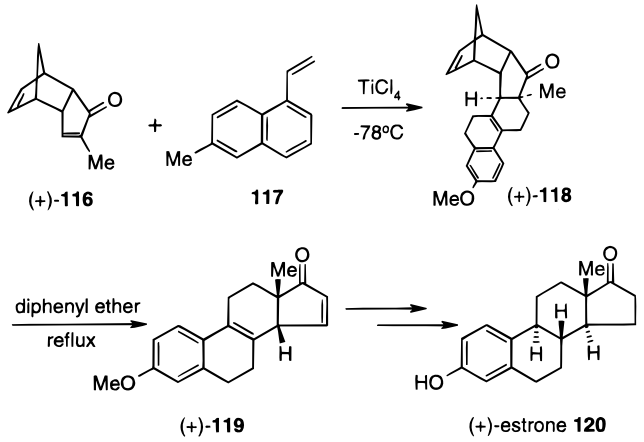
Scheme 32



tion and allylation followed by methylation proceeded stereoselectivily to afford *exo*-methyl ketone **112** in excellent yield. Thermal cycloreversion of **112** in refluxing *o*-dichlorobenzene gave cyclopentenone **113** in 90% yield without any racemization. Reduction of the enone double bond followed by oxidative cleavage of the vinyl bond and esterification led to cyclopentanone **114**, which is a known precursor for (+)-equilenin **115**. Starting from **113**, an alternative chiral route to (+)-**115** was developed as well.

Recently, (+)-estrone was prepared making use of the dienophilic activity of the enone double bond in the tricyclodecadienone system (Scheme 33).[49,50] Despite steric inhibition, this enone still has considerable dienophilic character in [4+2]-cycloadditions when catalyzed by strong Lewis acids. As shown earlier for the reaction of (−)-**15** with cyclopentadiene catalyzed by aluminum chloride, such [4+2] cyclization occurs with complete stereoselectivity from the *exo*-face of the cyclopentenone moiety.[51] Indeed,

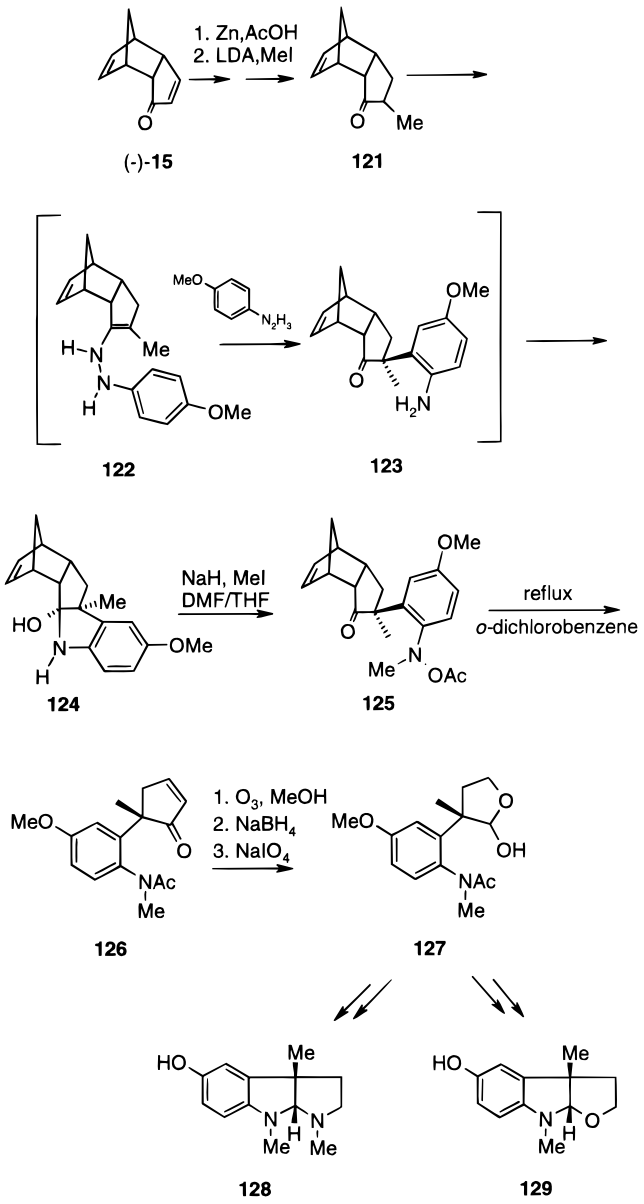
Scheme 33



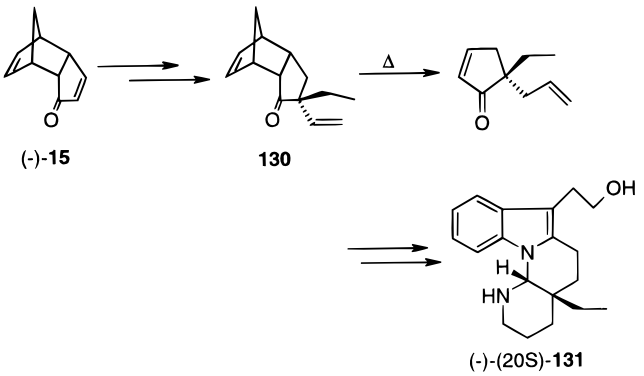
tricyclic enones (−)-**15**[49] and (+)-**116**[50] underwent a smooth reaction with Dane's diene **117** in the presence of diethylaluminum chloride or titanium(IV) chloride to afford regio- and stereoselectively the corresponding hexacyclic adducts, e.g., (+)-**118** from (+)-**116**, as single products in 75−80% yield. Cycloreversion of (+)-**118** in boiling diphenyl ether proceeded smoothly to the known tetracyclic compound (+)-**119**, which by previously reported procedures was converted into (+)-estrone **120**.

A fascinating application is certainly the enantiocontrolled total synthesis of the calabar bean alkaloids (−)-physovenine **128** and (−)-physostigmine **129** as a direct structural relationship between the tricyclodecadienone system and these alkaloids is not obvious (Scheme 34).[52] The key structure is cyclopentenone **126**, which in a series of ring-opening and ring-closure steps is converted in enantiopure hemiacetal **127**. This hemiacetal is then transformed into either (−)-physovenine **128** or (−)-physostigmine **129**. Starting from (−)-tricyclodecadienone **15**, reduction of the enone moiety followed by methylation gave an epimeric mixture of **121**, which by refluxing with *p*-methoxyphenylhydrazine was stereoselectively converted into carbinol amine **124** in 82% yield. This compound is probably formed by a [3,3]-sigmatropic rearrangement of the diaza-1,5-diene intermediate **122** to afford the imine **123** via introduction of the aryl group from the convex face of the molecule, followed by hydrolysis of the imine function. Acetylation and subsequent methylation of **124** produced tricyclic amide **125**, which on thermolysis in *o*-dichlorobenzene gave the above-mentioned cyclopentenone **126**. Interestingly, the necessity to find a synthetic route in which the absolute configuration of the quaternary stereogenic center in the target alkaloid molecules is unequivocally defined is apparently the reason for using the methodology pictured in Scheme 1. This same motif is also the origin of the enantiocontrolled total synthesis of natural (−)-goniomitine **131** (Scheme 35).[53] Starting from enantiomerically pure (−)-α,α-disubstituted tricyclotricyclodecenone **130** with known absolute configuration at the C_3-stereogenic center, the stereochemistry at C_{20} in the natural form of goniomitine could be unequivocally established. These last two examples show that the concept of transient chirality is applicable even for complex annulated systems which

Scheme 34



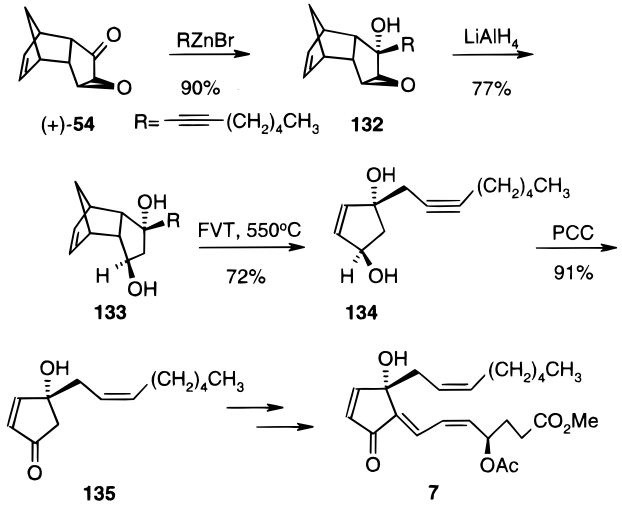
Scheme 35



are seemingly not related to the original polycyclic system or even not to the cyclic structure obtained after cycloreversion. The recent syntheses of (−)-kainic acid and the carbocyclic nucleoside (−)-neplanocin A are examples of enantioconvergent heterocyclic syntheses in which the relation between substrate and product is more apparent.[54,55]

Clavulones **7**, isolated from the Japanese soft coral *Clavularia viridis*, have interesting antitumor activity. Several groups have synthesized these marine prostanoids.[56] The approach used by the groups of Corey and Yamada is based on racemic or only partly resolved 4-hydroxycyclopentenone **135** as the key intermediate. Our alternative completely enantioselective synthesis of this intermediate is again based on a tricyclodecadienone epoxide, viz. homochiral (+)-**54** (Scheme 36).[57] Addition of zinc octynyl bromide

Scheme 36

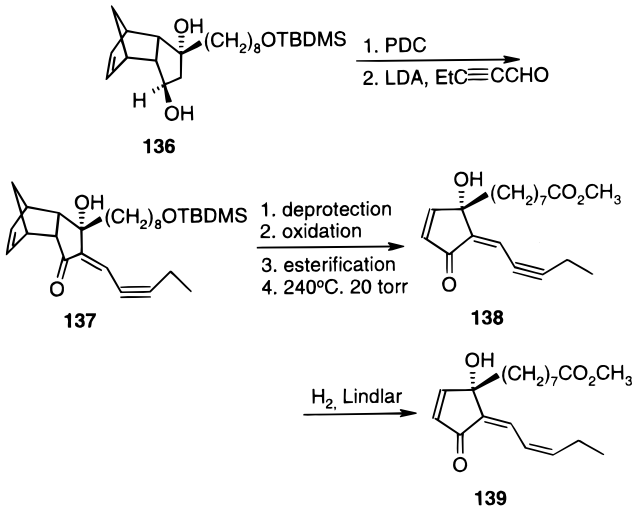


to (+)-**54** gave a chemo- and stereoselective reaction to produce alcohol **132** in nearly 90% yield. Subsequent regio- and stereoselective reductive opening of the epoxide function in **132** with lithium aluminum hydride in tetrahydrofuran led to the desired *trans*-1,3-diol **133** in good yield. Flash vacuum thermolysis of **133** at 550 °C and 0.05 Torr smoothly afforded cyclopentenediol **134** in 72% yield. Subsequent oxidation of **134** with pyridinium chlorochromate and stereoselective hydrogenation of the alkyne function using a Lindlar catalyst produced optically pure (−)-γ-hydroxycyclopentenone **135** in almost quantitative yield, thereby completing the formal synthesis of clavulones **7**. By starting from tricyclic ester (+)-**58** and using essentially the same approach, a series of clavulone analogues was prepared.[57]

In a similar manner, Liu et al. accomplished the synthesis of chromoric acid D I methyl ester **139**, although racemic (Scheme 37).[58] Chromomoric acids, isolated from *Chromolaens morii* and *C. chaslae*, are metabolites of linolenic acid. Their structures are very similar to the prostanoids clavulones. Starting from racemic **54**, 1,3-triol **136** was prepared similarly to **133** (Scheme 37). Oxidation to cyclopentanone followed by condensation with 2-pentynal gave enone **137**. Deprotection and oxidation of the terminal alcohol function gave the corresponding acid, which was then transformed into a methyl ester function. Gas flow thermolysis of this tricyclic ester gave cyclopentenone **138** in 64% yield. Stereoselective hydrogenation afforded *rac*-chromomoric acid D I methyl ester **139**. In an analogous way, chromoric acid C I was prepared.[59]

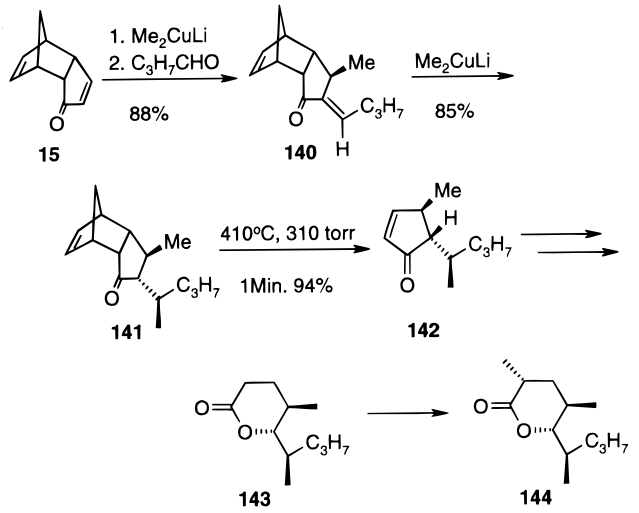
An interesting example of a double stereoselective Michael addition is encountered in the total synthesis

Scheme 37



of the queen recognition pheromone Invictolid **144** starting from tricyclic enone **15** (Scheme 38).[60] Ste-

Scheme 38

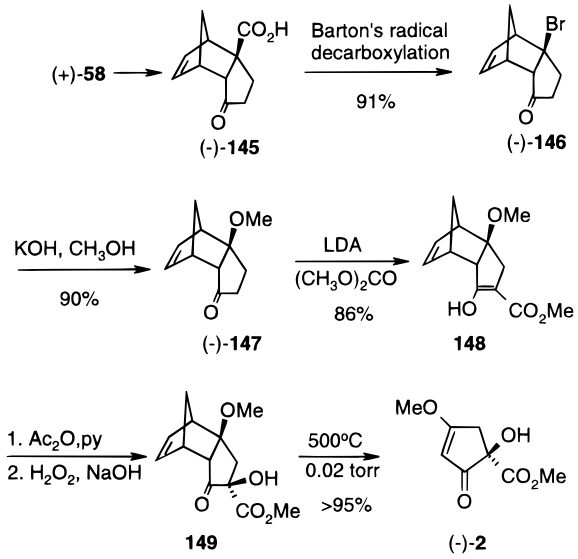


reoselective addition of dimethylcopperlithium to **15** followed by immediate trapping of the enolate with butenal gave, after spontaneous water elimination, *exo*-cyclic enone **140**. The introduction of the desired methyl group at the C_2-position in the butyl chain in invictolide **144** by conjugate addition of dimethylcopperlithium to *exo*-enone appeared again to be completely stereoselective and to occur from the *exo*-face of the cyclopentenone moiety, notwithstanding possible 1,3-interaction of the incoming cuprate with the initially introduced C_4-methyl group and the larger distance of the β-enone position to the annulated norbornene moiety. This result clearly illustrates the steric impact of the annulated norbornene moiety on additions on the cyclopentenone ring system in tricyclodecenones, which underscores the importance of the concept of transient chirality. Gas flow pyrolysis at 410 °C and 310 Torr afforded cyclopentenone **142** in high yield. Reduction of the enone double bond and subsequent Baeyer−Villiger oxidation afforded lactone **143**, which can be transformed in invictolide **144** by known procedures.

A final and quite illustrative example to be discussed in this comprehensive overview using the

tricyclodecadienone system as a transient chiral synthon constitutes the synthesis of kjellmanianone (**2**), a highly oxygenated cyclopentenoid isolated from brown algae *Sargassum kjellmanianum*. It was shown to possess moderate activity against gram-positive bacteria, such as *E. Coli* K12 and *Bacillus subtilis var niger*. The optical rotation of the natural product as isolated by Nakayama was remarkably low, viz $[\alpha]_D = +1.6°$ ($CHCl_3$).[61] Soon after its isolation, Smith et al. achieved an enantioselective synthesis of (+)-kjellmanianone by asymmetric hydroxylation of 3-methoxy-5-methoxy carbonyl-cyclopent-2-enone using enantiopure *N*-sulfonyloxaziridines in ee's up to 68.5%.[62] Although no enantiopure (+)-kjellmananione was obtained, its optical rotation was calculated to be $[\alpha]_D = \sim 100°$, showing that the natural product is largely racemic. Our route to enantiopure kjellmanianone **2** started from homochiral ethyl tricyclodecadienone 2-carboxylate (+)-**58** (Scheme 39).[63] Se-

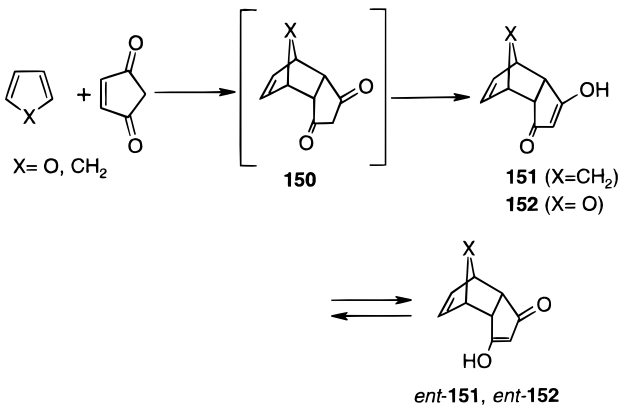
Scheme 39



lective reduction of the enone double bond at −78 °C, followed by alkaline hydrolysis, gave an almost quantitative yield of carboxylic acid (−)-**145**. Barton's halodecarboxylation procedure led to bridgehead bromide (−)-**146** in 91% yield. Replacement of the bromine function in **146** by a methoxy group was readily accomplished by reaction with potassium hydroxide in methanol to give (−)-**147** in 90% yield. Subsequent condensation of **147** with diethyl carbonate gave *β*-keto ester **148**, which appeared to be completely enolized. Acylation of **148** followed by peroxidation of the enol acetate with alkaline hydrogen peroxide gave the desired α-hydroxy-*β*-keto ester **149** in 70% yield. Epoxidation of enol acetate **148** was expected to occur from the sterically less hindered *exo*-face to give **149**. This structure was unambiguously ascertained by an X-ray analysis. In the final step, enantiopure (−)-kjellmanianone **2** was produced in high yield by thermal cycloreversion by flash vacuum thermolysis of **149** at 500 °C and 0.02 Torr. The *R* configuration of synthetic (−)-kjellmanianone proved that the previously assigned absolute configuration of (+)-kjellmanianone by exciton chirality methodology is incorrect.

A most convenient and direct route to the tricyclodecadienone system **12** is the Diels−Alder reaction of cyclopentene-1,3-dione with cyclopentadiene or furan (Scheme 40).[64] Interestingly, the adduct **150**

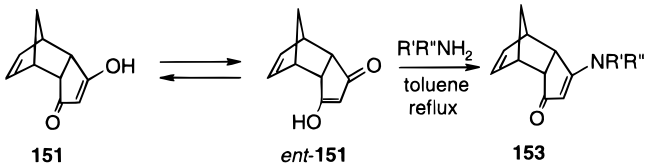
Scheme 40



is completely enolized and actually consists of a racemic and rapidly equilibrating mixture of antipodes **151** and *ent*-**151** or **152** and *ent*-**152**. This fast enantiomerization of these tricyclic enols, in principle, allows a dynamic kinetic resolution, possibly leading to the formation of a single enantiomer or diastereomer. For enols **151** and **152**, such a process could also be denoted as an asymmetric desymmetrization of a *pseudo-meso* compound. If successful, this route would considerably contribute to the synthetic merit of the methodology depicted in Scheme 1.

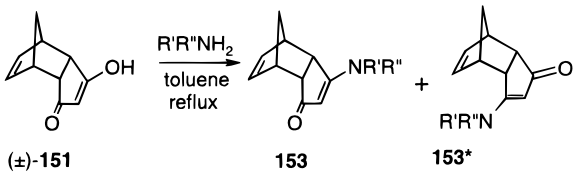
Attempts to achieve a desymmetrization or a dynamic kinetic resolution of **151** using enzymes failed.[65] Enantioselective acylation of **151** using a variety of enzymes did not lead to the corresponding enol acetates. A reason of this failure may be the poor solubility of **151** in organic solvents. After having discovered that tricyclic enols **151** can be readily transformed into enaminones **153** with a variety of amines (Scheme 41),[65] chiral amines were applied for

Scheme 41



dynamic kinetic resolution of **151**. Whereas *R*-(+)-α-phenylethylamine gave a good yield of enaminones **153a** and **153a*** but with no diastereoselectivity at all, a satisfactory result was obtained when L-prolinol was applied (Scheme 42).[65] Enaminone **153b** was obtained in an overall yield of 91% and with a diastereomeric excess of 50%. Separation of the two diastereomers was most conveniently achieved via their acetates. Other prolinol derivatives gave similar results. The absolute stereochemistry of the major diastereomer was shown by X-ray diffraction analysis

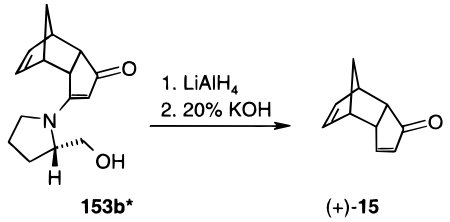
Scheme 42



R'R"NH:	ratio of diastereomers		yield
a (R)-(+)-α-phenylethylamine	1	1	80%
b (S)-(+)-prolinol	1	3	91%
c (S)-(+)-prolinol methyl ether	1	3	79%
d (S)-(-)-methyl prolinate	1	1.8	94%

to be **153b***. Reductive elimination of the chiral auxiliary in **153b*** with lithium aluminum hydride afforded optically pure parent tricyclodecadienone (+)-**15** in good overall yield (Scheme 43). Although

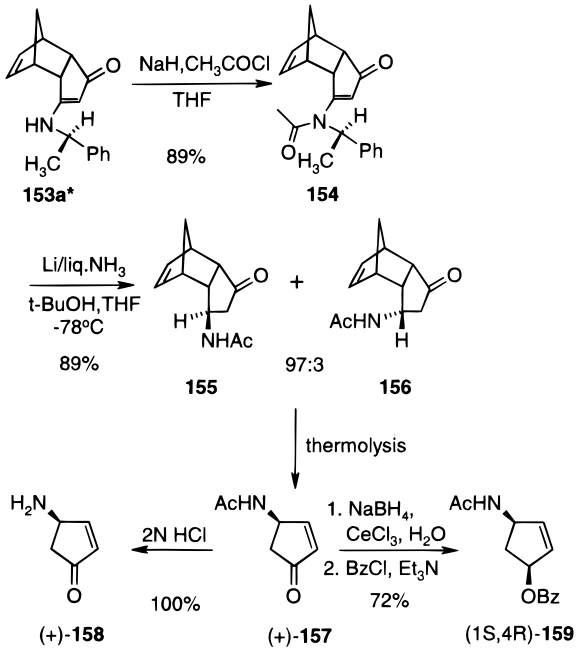
Scheme 43



complete diastereoselectivity was not attained, this asymmetric desymmetrization of **151** is a novel and attractive alternative for the existing enzymatic methodology to obtain enantiopure tricyclodecadienones. In addition, the tricyclic enaminones **153** are conceivable chirons for nitrogen-containing cyclopentanoids.

Although not leading to any diastereoselectivity, the (*R*)−(+)-α-methylbenzylamine adduct of **151** could be conveniently and efficiently separated by crystallization to give both **153a** and its diastereoisomer **153a*** enantiomerically pure. Both these enaminones were utilized for an enantioselective route to 4-*cis*-acetylaminocyclopentenols, which are the precursors for 5′-norcarbocyclic nucleosides (Scheme 44).[66,67] Although a wide variety of hydride reagents have been employed for the reduction of the enaminone double bond, none of them proved successful. The conventional reagents either refused to reduce the enaminone double bond in **153** or if reduction had occurred the resulting *β*-amino ketone underwent immediate elimination of the main functionality to give the parent tricyclo[5.2.1.$0^{2,6}$]decadienone. Although acylation of the amino function promoted the hydride reduction, unequivocal reduction of the enone double bond in **154** could still not be accomplished satisfactorily. A highly rewarding result was, however, obtained when an electron-transfer-type reduction with lithium in liquid ammonia in the presence of *tert*-butyl alcohol as the proton donor was attempted. A mixture of diastereomeric *β*-amino ketones **155** and **156** was obtained from **154** in excellent yield (89%) and with a remarkably high diastereoselectivity (*de* 94%). This reduction of the enaminone double bond along with the concomitant removal of the chiral auxiliary by lithium in liquid ammonia is unprecedented. It is worth

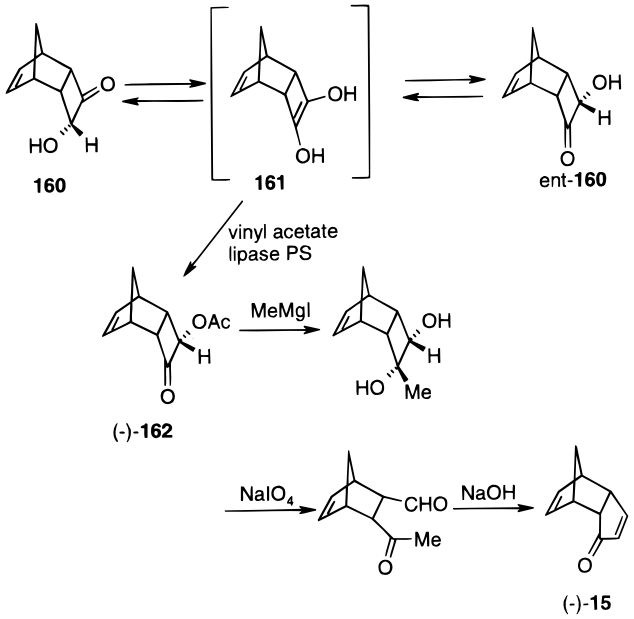
Scheme 44



noting that despite the *endo*-face being sterically considerably hindered in **154**, proton donation at C_5 preferentially occurs from the *endo*-face, thus positioning the *β*-amino group on the *exo*-side. Interestingly, the reduction of the diastereomer of **154** similarly gave a high yield of *ent*-**155** and *ent*-**156**, however, with considerably lower diastereoselectivity (*de* 76%). This difference in diastereoselectivity indicates that the chiral α-methylbenzyl group plays a pronounced role in determining the stereochemistry of protonation of the intermediate carbanion. It may therefore be concluded that the reduction of the enone moiety precedes the reductive removal of the α-methylbenzyl group. As separation of the diastereomers **155** and **156** was not easy, the mixture (*de* 94%) was subjected to thermolysis under static conditions in refluxing *o*-dichlorobenzene as well as under flash vacuum thermolytic conditions (0.05 mbar, 500 °C) to give (*R*)−(+)-*N*-acetyl-4-aminocyclopentenone **157** in about 90% yield. The enantiomeric excess in both cases amounted to 94%, showing that under static and dynamic thermolysis practically no racemization had occurred. Removal of the *N*-acetyl group was readily accomplished by hydrolysis in 2 N aq HCl to yield (*R*)−(+)-4-aminocyclopentenone **158** as its hydrochloride. The route to an appropriate *cis*-3-aminocyclopentenol derivative was completed by selective 1,2-reduction of the carbonyl group in **157** utilizing the Luche reduction followed by benzoylation of the alcohol to give (−)-**159**.[67] This last-mentioned compound had already been applied for the synthesis of carbanucleosides.

A second case of a dynamic kinetic resolution involving a *pseudo*-meso polycyclic structure, eventually leading to enantiomerically pure parent tricyclodecadienone **15**, has recently been reported by Ogasawara et al (Scheme 45).[68] During the preparation of racemic tricyclic acyloin **160** from *endo*-2,3-bis(methoxycarbonyl)bicyclo[2.2.1]hept-5-ene, only the *endo*-alcohol **160** was isolated because of a selective

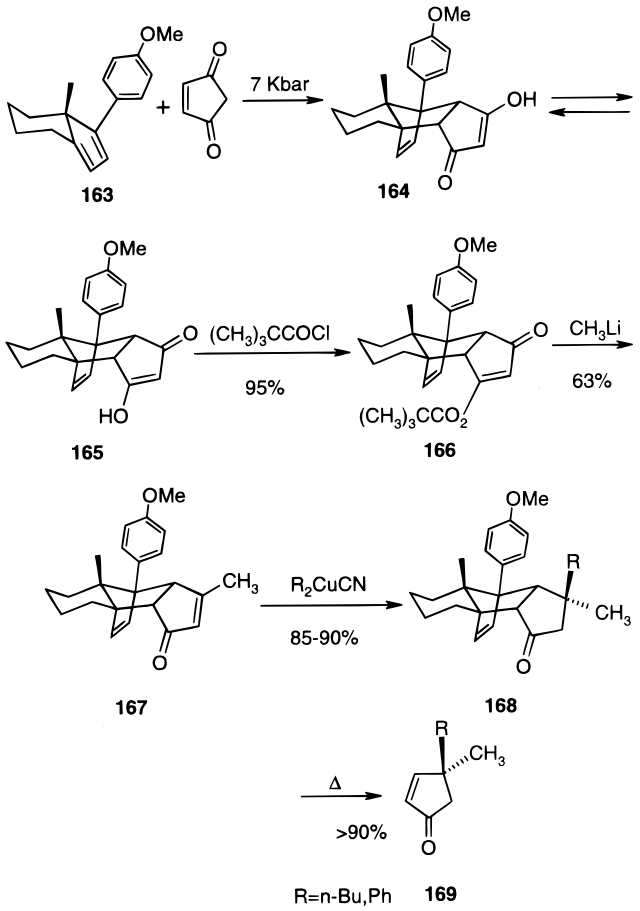
Scheme 45



protonation of the convex face of the transient *meso*-1,2-diol **161**. A dynamic kinetic resolution was now realized by subjecting *rac*-**160** to an enzymatic esterification applying lipase PS and vinyl acetate as the acyl donor in the presence of triethylamine. Optically pure *endo*-acetate (−)-**162** was produced in 75% yield, demonstrating the chiral efficiency of this process. When the enzymatic transesterification was carried out in the absence of triethylamine, simple kinetic resolution occurred to give the same *endo*-acetate with the same high optical purity (>99% ee) but in only 45% yield and leaving 53% of the optically enriched starting acyloin (+)-**160**. Thus, triethylamine is promoting the equilibration of the enantiomers of **160** via *meso*-diol **161**, allowing the asymmetric transformation in the presence of this base. In a three-step procedure (−)-acetate **162** was converted in tricyclodecadienone (−)-**15** in 50% overall yield (Scheme 45). So far the concept of transient chirality for the synthesis of cyclopentanoids has been illustrated for relatively simple tricyclic systems which are the Diels−Alder adducts of an appropriate dienophile and an achiral diene. Both resolution and asymmetric synthesis have then been used in order to achieve efficient access to these tricycles in enantiopure form. In the mid-1980s Winterfeldt[69] realized that homochiral cyclopentadienes could be suitable structures to obtain homochiral polycyclic compounds which could then be utilized as transient chiral intermediates in a Diels−Alder/retro-Diels−Alder fashion as depicted in Scheme 1. In addition, the conceivable use of these homochiral dienes to achieve kinetic resolution of chiral dienophiles was investigated.[70]

Using readily accessible and configurationally well-defined enantiopure dienes such as steroid and hydrindan dienes in combination with appropriate achiral dienophiles, the corresponding polycyclic adducts are generally obtained in excellent yields and with high stereo- and enantioselectivity. The applicability of these adducts as transient chiral intermediates is illustrated by several examples.[70] A recent example showing the potential of this approach for the synthesis of cyclopentanoids is given in Scheme 46.[71] Reaction of cyclopentene 1,3-dione

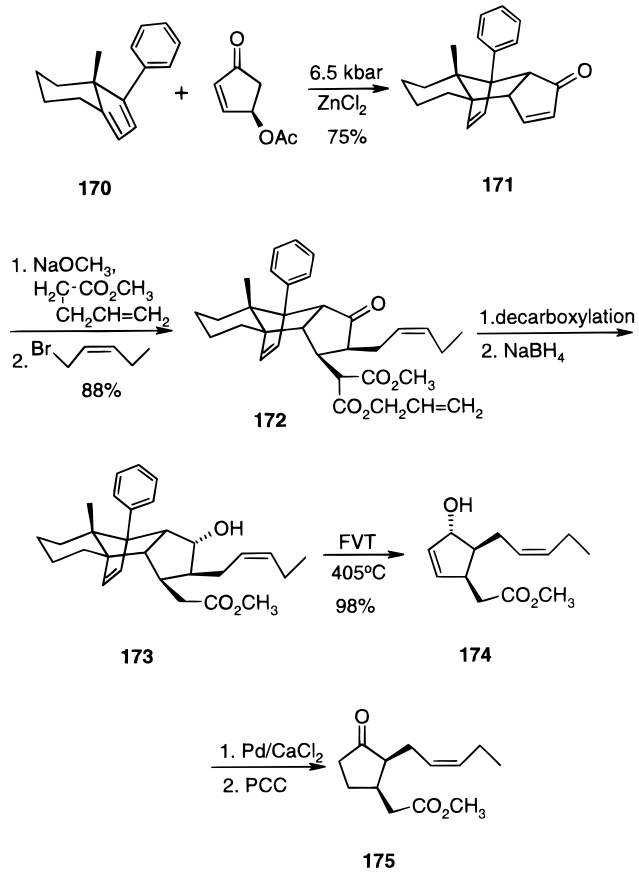
Scheme 46



with enantiopure cyclopentadiene **163** under high pressure leads to a mixture of diastereomeric enols **164** and **165**, which by treatment with pivaloyl chloride affords preferentially enol ester **166** for steric reasons. Subsequent addition of organolithium compounds produces β-alkylated enones, however, only if the phenyl group in **166** contains a *para*-methoxy group. In the absence of such a methoxy group, the pivaloyl group is attacked by the organolithium reagent to regenerate the enols **164** and **165**. This effect is denoted as electron density directed regioselectivity.[71] Cuprate additions to **167** gave stereoselectively dialkylated **168**, which on thermolysis gave the enantiomerically pure cyclopentenones **169**.

Another recent example is the synthesis of (−)-methyl cururbate **174** and (−)-methyl jasmonate **175** using diene **170** and 4-acetoxycyclopentenone, both enantiopure (Scheme 47).[72] The enantiopure tetracyclic enone **171** is obtained in excellent yield. Subsequent 1,4-addition and electrophilic substitution proceeds completely stereoselective to give **172**, which in a two-step procedure is transformed in β-alcohol **173**. Gas-phase thermolysis at 405 °C produces methyl dehydrocucurbate **174**. Selective catalytic reduction of **174** followed by oxidation affords (−)-methyl jasmonate **175**.

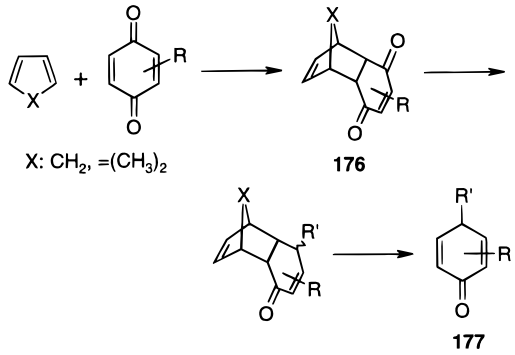
Scheme 47



III. Cyclohexanoids

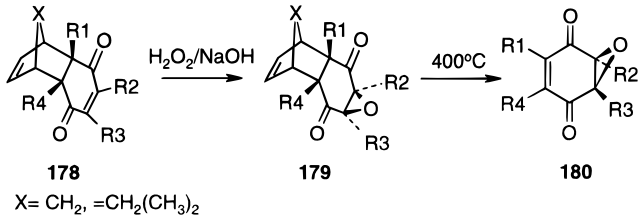
The utilization of the *endo*-tricyclo[6.2.1.0^{2,6}]undecadienedione system **176** as a transient chiral intermediate for the stereoselective synthesis of cyclohexenoids **177** (Scheme 48) was reported much earlier

Scheme 48



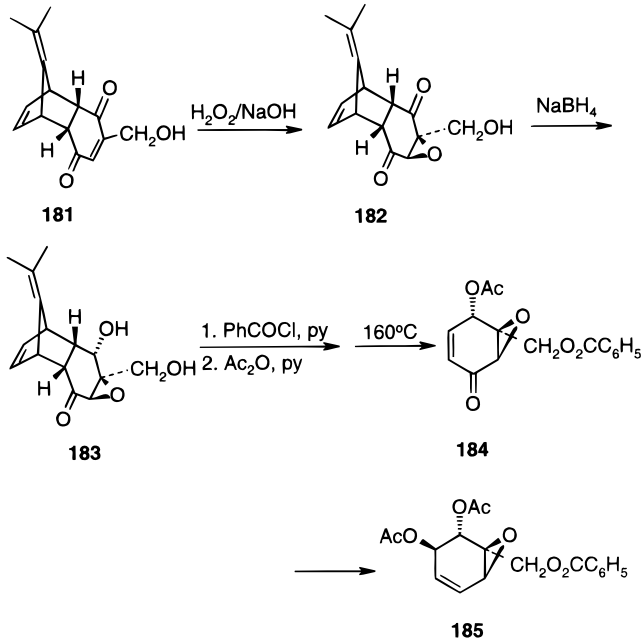
than that of the tricyclo[5.2.1.0^{2,6}]decenone system **12** (Scheme 1). This is mainly due to the ample availability of **176** by simple Diels−Alder reaction of cyclopentadiene or fulvenes with benzoquinones. A first example is the stereoselective synthesis of benzoquinone epoxides **180** by nucleophilic epoxidation of **178**, followed by thermal cycloreversion of tricyclic epoxide **179** (Scheme 49).[73] In all cases, epoxidation occurs exclusively from the sterically less hindered *exo*-face. However, after this first interesting report, it took about 15 years before this route to epoxycyclohexenoids was further developed by the

Scheme 49



group of Ichihara for the synthesis of naturally occurring highly oxygenated cyclohexanoids.[74−76] They showed that an efficient and clean cycloreversion of epoxides **179** to the corresponding monocyclic epoxides **180** could only be accomplished by using the dimethylfulvene adduct of benzoquinones. The cycloreversion of such fulvene adducts **179** [X = C=C(CH$_3$)$_2$] generally proceeds at considerably lower temperatures than that of the corresponding cyclopentadiene adducts **179** (X = CH$_2$). However, in contrast to the cyclopentadiene/benzoquinone cycloaddition, *endo*-stereoselectivity is not complete when fulvene is used as the diene and generally some *exo*-adduct is also obtained. Epoxidation of both the *endo*- and *exo*-adduct is again completely stereoselective. The synthesis of *rac*-senepoxide **185** is a typical demonstration of this approach (Scheme 50).[77]

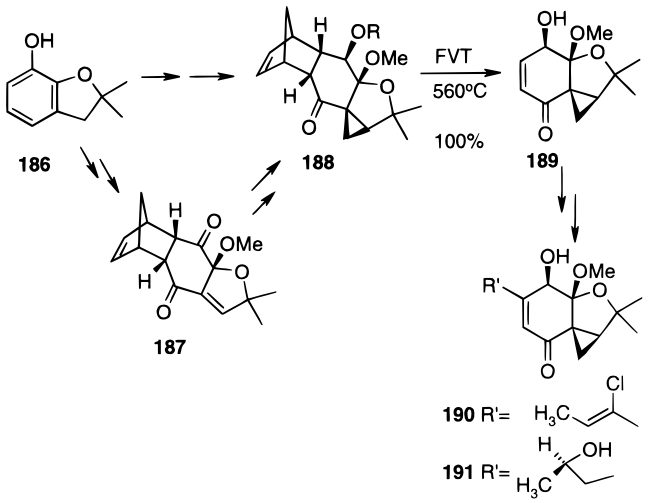
Scheme 50



Starting from *endo*-benzoquinone adduct **181**, basic epoxidation affords epoxide **182** stereoselectively, which regio- and stereoselectively gives alcohol epoxide **183** upon reduction with sodium borohydride. Selective acetylation and benzoylation of the hydroxylic groups, followed by thermolysis in diglyme at 160 °C, produces cyclohexenone **184** in 78% yield. Epoxidation of the enone moiety in **184** followed by hydrazine-mediated eliminative epoxide ring opening and subsequent acetylation concludes this synthesis of synepoxide **185**. Other bioactive naturally occurring cyclohexene epoxides that are synthesized in this way are phyllostin, epoxydione, epi-epoxydone, epi-epoformin, and epoformin.[78]

A key intermediate for the synthesis of racemic mycorrhizin A (**190**) and gilmicolin (**191**) was synthesized by Brown et al. applying benzoquinone adduct **187**, which is readily prepared from commercially available benzofuranol **186** (Scheme 51).[79]

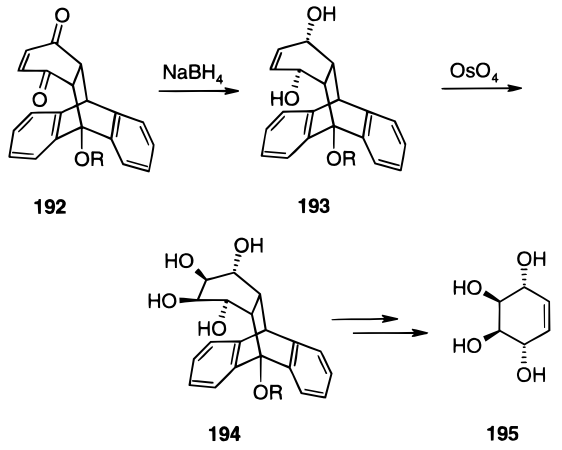
Scheme 51



In a few steps **187** is stereoselectively transformed into pentacyclic dione **188**, which on flash vacuum thermolysis at 560 °C and 0.1 Torr leads to the known precursor **189** for **190** and **191** in essentially quantitative yield.

The use of an anthracene/benzoquinone adduct for the first stereoselective synthesis of the naturally occurring cyclitol conduritol A (**195**) is depicted in Scheme 52.[80] The 9-oxygenated anthracene adduct

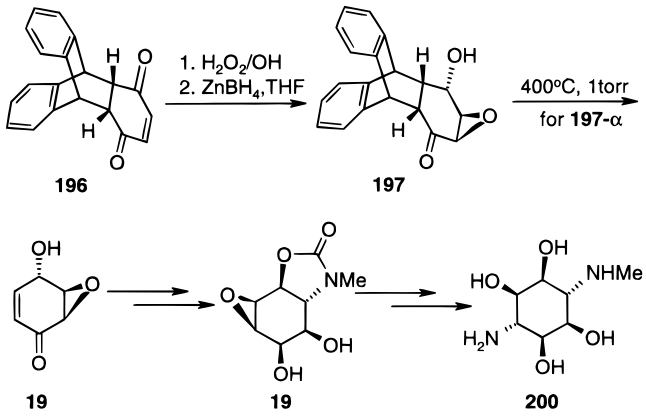
Scheme 52



192 is used in order to profit from the accelerating effect of the oxido group on the [4+2]-cycloreversion. Sodium borohydridecerium(III) chloride reduction of **192** stereoselectively afforded *cis*-diol **193**. Dihydroxylation of **193** was carried out with osmium tetraoxide to give tetrol **194**, again with complete stereoselectivity. After removal of the bridgehead benzyloxymethoxy protecting group, followed by protection of the secondary hydroxyls on the six-membered ring as the acetonide and benzyloxy ethers, cycloreversion was accomplished at room temperature by treatment with sodium hydride in dioxane. Subsequent deprotection of the initially formed oxygenated cyclohexene afforded racemic conduritol A (**195**) in 39% overall yield from benzoquinone. A few years later, a considerably more efficient approach to conduritol A was published. Essentially, the same methodology is used but it avoids the protection/deprotection sequence.[81] Instead of using 9-(benzyloxy)methoxyanthracene as the diene, anthracene itself was applied. The cycloreversion was eventually accomplished by applying flash vacuum thermolysis. The overall yield of conduritol-A (**195**) from benzoquinone was increased to 72%.

Along the same line, the formal total synthesis of 3-*O*-demethylfortamine (**200**) was realized (Scheme 53).[82] Stereoselective alkaline epoxidation of the

Scheme 53

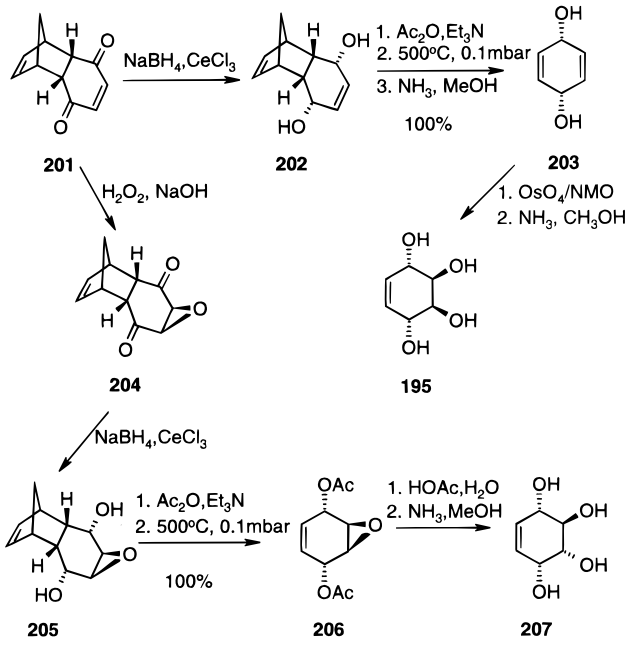


anthracene adduct **196** followed by a not completely stereoselective partial reduction with zinc borohydride in THF afforded a mixture of α- and *β*-alcohols **197**. When subjected to flash vacuum thermolysis at 400 °C, α-**197** produced cyclohexenone **198** in 92% yield. Subsequent group transformations led to lactone **199**, which is a known precursor for **200**, in 33% overall yield.

Recently, both conduritol A (**195**) and F (**207**) were prepared from the cyclopentadiene adduct of benzoquinone **201** (Scheme 54).[83] The basis of this approach is the stereoselective synthesis of oxygenated cyclohexa-1,3-dienes viz. **203** and **206** which either by bishydroxylation or hydrolysis are stereoselectively transformed in the respective natural products. Both for tricyclic dione **201** and its epoxide **204** the hydride reduction using Luche's reagents appeared highly stereoselective and gave the corresponding *endo,endo*-diols **202** and **205** in high yields. Acetylation followed by flash vacuum thermolysis produced **203** and **206** in quantitative yield. The high-yield syntheses of these cyclohexenes is illustrative for the potential of the flash vacuum thermolysis technique as these compounds are kinetically rather unstable and rapidly aromatize. Conventional preparation methods to obtain these compounds are therefore not suitable.

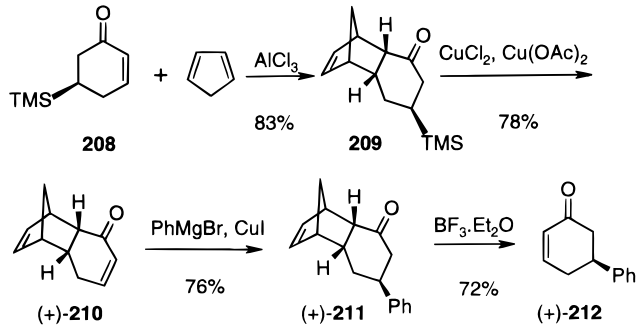
So far all the examples mentioned above have dealt with racemic material, and it is obvious that full advantage of the concept of transient chirality is obtained when access to the diene adducts can be accomplished in an enantioselective manner for the ultimate preparation of enantiomerically pure cyclo-

Scheme 54



hexenoids. A first approach constitutes the asymmetric Diels−Alder reaction of enantiopure 5-trimethylsilylcyclohexenone **208** with cyclopentadiene catalyzed by aluminum chloride (Scheme 55).[84] A

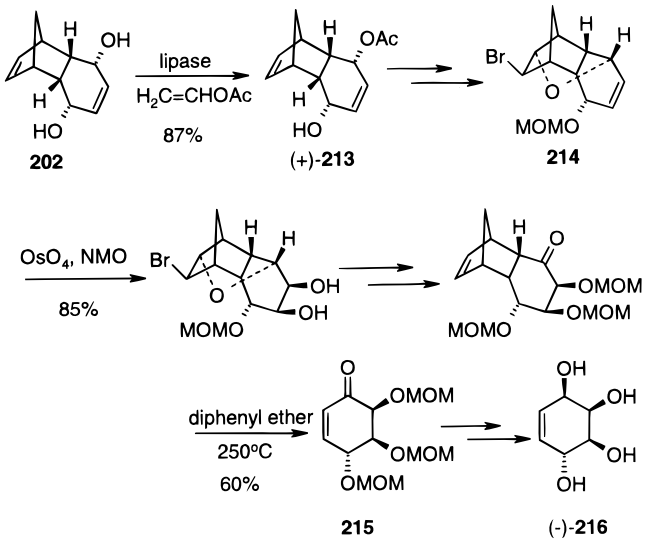
Scheme 55



mixture of *endo*- and *exo*-adduct **209** is obtained in 83% yield with an *endo*/*exo* ratio of 13.5:1. The major product *endo*-**209** was readily isolated from the mixture and considered to be of high optical purity. Oxidative elimination of the trimethylsilyl group with copper dichloride completed the first enantioselective synthesis of homochiral tricyclo[6.2.1.$0^{2,7}$]undecadienone **210**. To exemplify the potential of this tricyclic enone as a chiral cyclohexenone synthon, the copper(I)-catalyzed 1,4-addition of phenylmagnesium bromide to (+)-**210** was studied. Addition proceeded smoothly and stereoselectively to give (+)-**211**. The retro-Diels−Alder reaction catalyzed with BF_3 etherate gave (S)-(+)-5-phenyl-2-cyclohexen-1-one (**212**) with high optical purity and an acceptable overall yield.

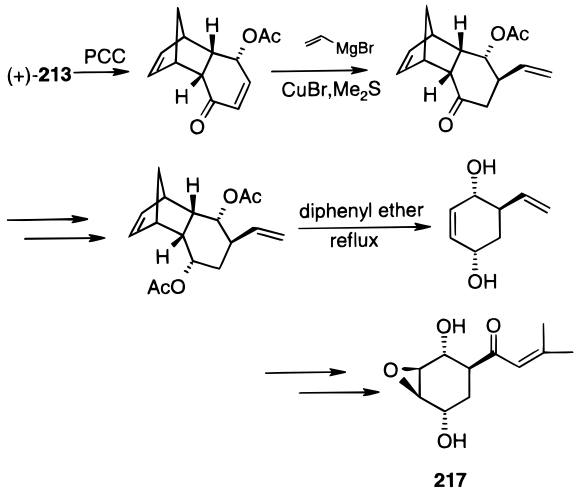
Undoubtedly triggered by the successful enzymatic kinetic resolution and desymmetrization of the tricyclodecadienone system **89**, as reviewed in the last section (Scheme 24), Takano and Ogasawara investigated the possible desymmetrization of *endo*,*endo*-1,4-diol **202** (Scheme 56).[85] Incubation of **202** with

Scheme 56



lipase PS in acetonitrile and in the presence of vinyl acetate produced the optically pure monoacetate (+)-**213** in 87% yield after 2 weeks. This chiron was then applied to the synthesis of (−)-conduritol C (**216**) as depicted in Scheme 56. As explained earlier in Scheme 26, the norbornene double bond was temporarily protected in the same way in order to allow stereoselective bishydroxylation of the cyclohexene double bond in **214**. Deprotection and cycloreversion produced the optically pure cyclohexenone **215**, which after a stereoselective reduction and subsequent deprotection was transformed into conduritol C (**216**). Using the same chiron (+)-**213**, the fungus metabolite eutypoxide B (**217**) was prepared (Scheme 57).[86] The

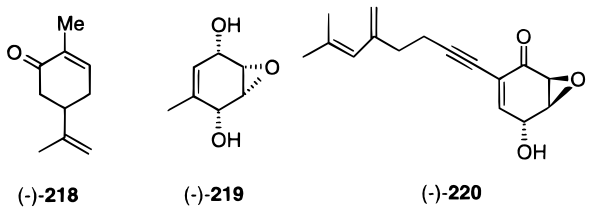
Scheme 57



complexity of this last structure containing five stereogenic centers again clearly demonstrates the synthetic merit of the concept of transient chirality outlined in Scheme 1.

Other examples of enantioselective natural product syntheses starting from (−)-**213** are the synthesis of (−)-carvone (**218**),[87] (−)-theobroxide (**219**),[88] and (−)-tricholomenyn A (**220**), Figure 2.[89]

An interesting modification of the enzymatic desymmetrization of tricyclic diol **202** is the homoge-

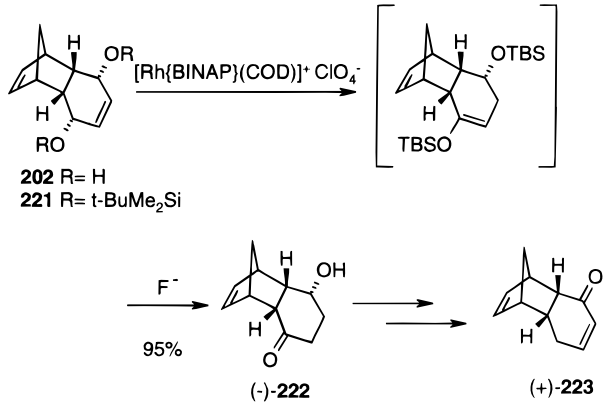


(-)-**218** (-)-**219** (-)-**220**

Figure 2.

neous catalytic desymmetrization which is based on the olefinic isomerization of *meso*-**202** to γ-hydroxyketone **222** using [Rh{chiral-BINAP}(COD)]$^{+}$ClO$_4^{-}$ (Scheme 58).[90] Optimum results were obtained with

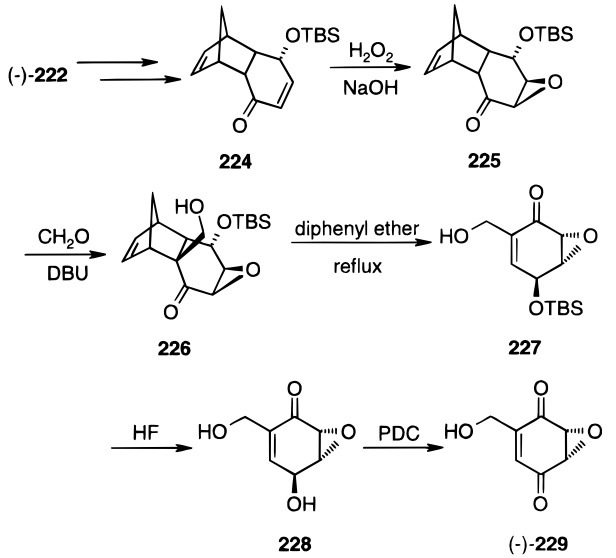
Scheme 58



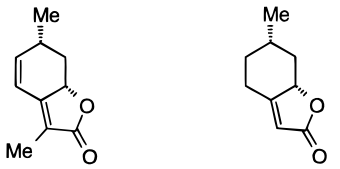
(-)-**222** (+)-**223**

the bis(silyl) ethers **221** which gave the γ-hydroxyketone (−)-**222** after desilylation in 95% chemical yield and an excellent optical purity of 96%. By appropriate functional group transformations, (−)-**222** was converted in enantiopure tricyclic enone (+)-**223**. This access to homochiral tricycloundecenones was used for the synthesis of some polyoxygenated cyclohexenemethanols, viz. (+)-epi-epoxydon (**228**) and (−)-phyllostine (**229**) (Scheme 59).[91] In a few

Scheme 59



steps, (−)-**222** was converted in silyl ether **224**, which was regio- and stereoselectively epoxidized to **225** in the usual way. Condensation with formaldehyde to **226** followed by thermolysis in boiling diphenyl ether gave the protected cyclohexenone **227** in excellent yield. Subsequent desilylation gave enantiopure (+)-epi-epoxydon (**228**), which on selective oxidation with pyridinium dichromate gave (−)-phyllostine (**229**). Both compounds were completely identical to their natural counterparts. Quite recently, the same methodology was applied for the enantioselective syntheses of the important commercial aroma compounds (+)-mintlactone (**230**) and (+)-isomintlactone (**231**), Figure 3.[92]

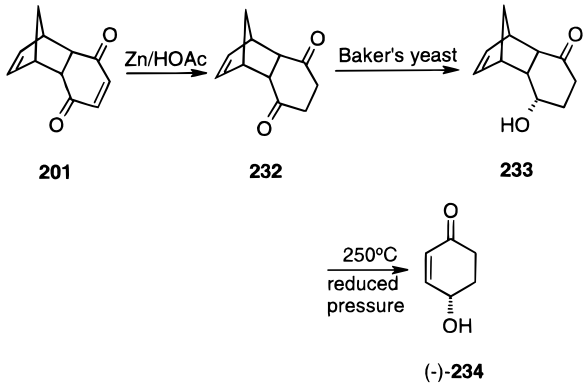


(+)-**230** (+)-**231**

Figure 3.

The importance of enantiopure 4-hydroxy-cyclohex-2-en-1-one **234** as the starting material for the synthesis of the compactin−mevinolin family of natural products prompted Marchand et al. to investigate the Baker's yeast promoted reduction of tricyclic *meso*-dione **232**, which is readily accessible from **201** by zinc reduction in acetic acid (Scheme 60).[93] The yeast reduction was not completely regio-

Scheme 60

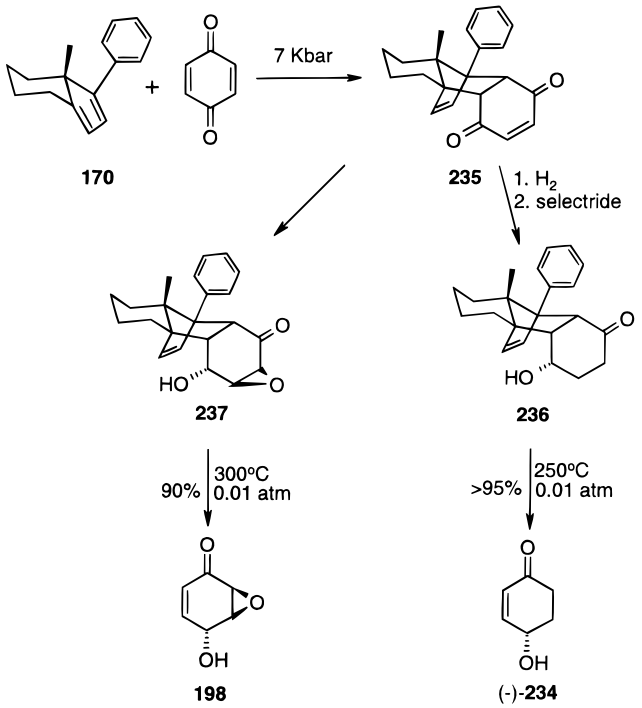


(-)-**234**

and stereoselective and gave a mixture of four optically active isomeric ketols among which **233** dominated (32% yield). Gas flow thermolysis gave (*S*)−(−)-**234** with high stereoselectivity but moderate enantioselectivity (64% ee).

Winterfeldt et al. prepared (−)-**234** using his well-known homochiral diene **170** (Scheme 61).[94] Benzoquinone addition to **170** applying high-pressure yields *endo*-adduct **235** in 95% after 3 days reaction time. Adduct **235** was relatively unstable at room temperature and is prone to undergo cycloreversion. Regioselective hydrogenation followed by regio- and stereoselective hydride reduction gave *endo*-alcohol **236**. Cycloreversion of **236** was carried out in the Kugelrohr apparatus at 250 °C to give (−)-**234** in almost quantitative yield. The corresponding epoxy cyclohexenone **198** was prepared from benzoquinone adduct **235** by stereoselective peroxidation of the ene−dione double bond followed by regio- and stereoselective L-selectride reduction to give epoxy alcohol **237** (Scheme 61).[95] Flash vacuum thermolysis of **237**

Scheme 61



at 300 °C at 0.01 atm gave **198** in 90% yield. Other examples of homochiral cyclohexenones prepared recently using the same approach are **238**, **239**, and **240**, Figure 4.[96]

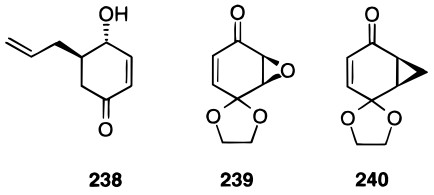
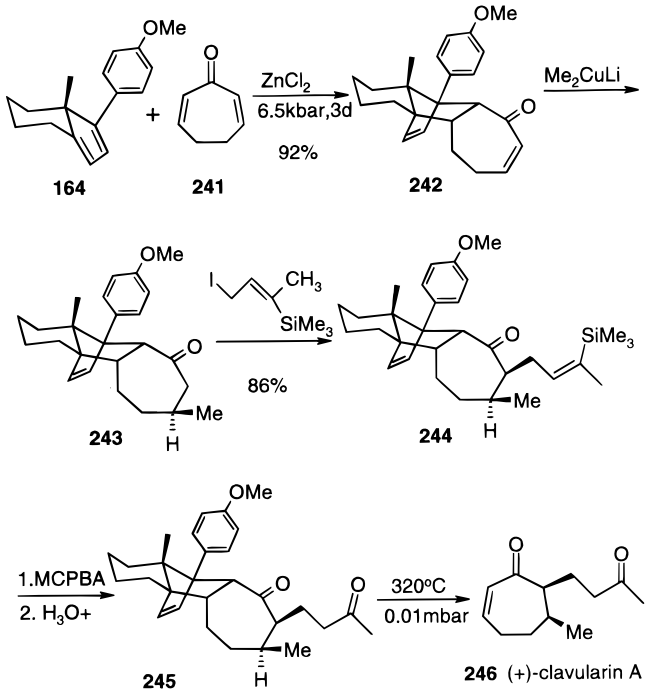


Figure 4.

This paragraph is concluded by the only example of a cycloheptenoid synthesis known so far which makes use of the concept of transient chirality. To accomplish a complete enantioselective route to the biologically interesting clavularins, e.g., (+)-clavuranine A (**246**), which have cytotoxic properties, the Diels−Alder adduct **242** of cycloheptadienone **241** with homochiral diene **164** was examined for the stereoselective introduction of the methyl and butanone groups present in clavuranin A (Scheme 62).[97] Despite the relatively flexible seven-membered ring, the subsequent 1,4-cuprate addition proceeded with complete stereoselectivity to afford exclusively **243**. The desired *cis*-butanone group was introduced via vinylsilane substitution at the α-position, which also appeared to be completely stereoselective to yield *cis*-disubstituted **244** in 86%. The well-known epoxidation−hydrolysis sequence subsequently gave diketone **245** in 81% yield. Finally, flash vacuum thermolysis at 320 °C gave enantiomerically pure (−)-clavulurin A (**246**) in 91% yield. These first results with a cycloheptadienone adduct show that the diastereoselectivity of addition and substitution reactions to this more relaxed system is as high and reliable as

Scheme 62

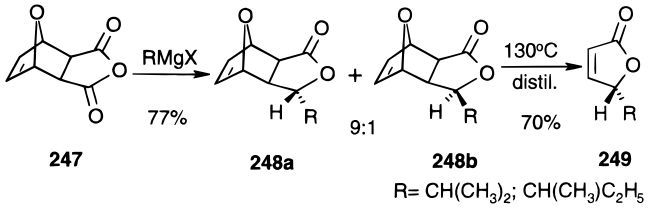


with the corresponding five- and six-membered-ring systems, thus again following the concept of transient chirality.

IV. Heterocyclic Five-Membered Ring Compounds

Chiral five-membered hydrofuran and pyrrolidine systems are important structural entities in many natural and pharmaceutically interesting compounds. In addition, they are useful intermediates for the synthesis of acyclic structures. Many synthetic routes to these heterocycles have been successfully designed and applied. A first attempt to use the Diels−Alder/retro-Diels−Alder methodology (see Scheme 1) and taking advantage of the transient chirality of the initially formed polycyclic structure was reported in 1981 by Canonne et al. who prepared chiral 4-substituted butenolides **249** starting from the Diels−Alder adduct **247** of furan and maleic anhydride (Scheme 63).[98] Addition of Grignard reagents oc-

Scheme 63

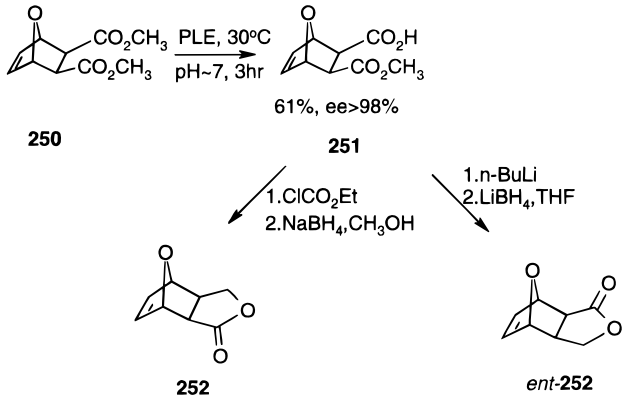


curred stereoselectively from the sterically less hindered convex face of **247** to give preferentially the *exo*-isomer **248a** (ratio *exo*/*endo* 9:1). Distillation of **248** at 130 °C gave butenolide **249** in about 70% overall yield.

The finding that bicyclic *meso*-diester **250** is an excellent substrate for pig liver esterase to give half-ester **251** prompted Bloch et al. to explore homochiral

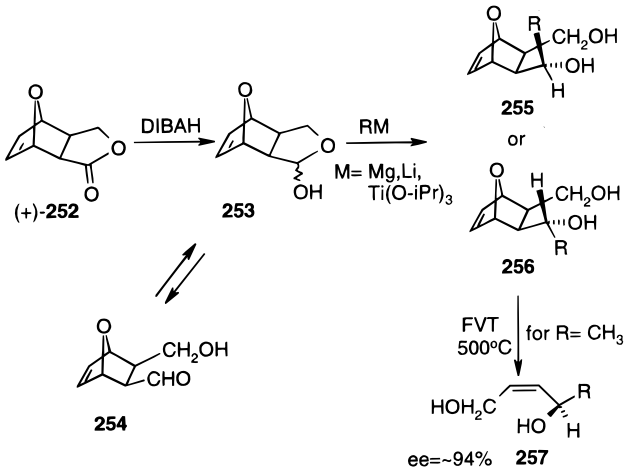
oxatricyclic lactones **252** as chirons. (Scheme 64).[99]

Scheme 64



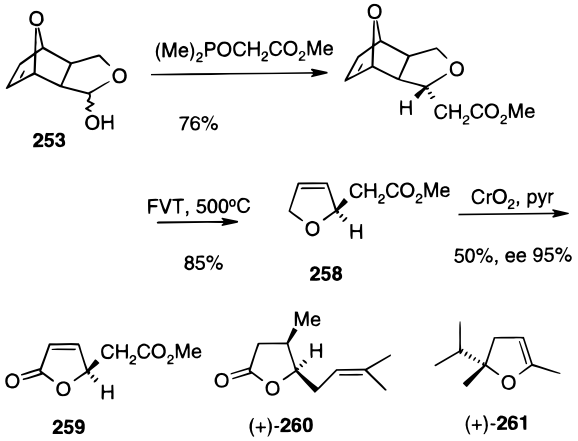
Both antipodes of **252** are readily available from **251** by choosing the right reduction sequence. The stereoselective and enantioselective synthesis of allyl alcohols **257** via lactones **252** shows the synthetic potential of this approach (Scheme 65).[100] Reduction

Scheme 65



of **252** with di-*i*-butylaluminumhydride gave lactol **253**, which was converted into tricyclic diols **255** or/and **256** with a high degree of stereoselectivity by addition of the organometallics to the initially formed hydroxyaldehyde **254**. The stereoselectivity observed in these additions is strongly dependent on the nature of the metal and the solvent used because of bidentate or tridentate chelation of the metal cation with the bridgehead oxygen, the aldehyde carbonyl oxygen, and the methanol oxygen. Flash vacuum thermolysis of **256** at 500 °C gave the allyl alcohol **257** in high optical purity. Another illustrative example is the synthesis of an optically active dihydrofuran derivative **258** via a completely stereoselective tandem Wittig−Michael addition to homochiral lactol **253** (Scheme 66).[101] Oxidation of **258** with CrO_3 in pyridine gave the naturally occurring butenolide **259** with an ee of 95%. In a similar way, the syntheses of (+)-eldanolide (**260**), the sex pheromone of *Eldana saccharina*, and (*S*)−(+)-4,5-dimethyl-4-hexanolide (**261**), the precursor for a sex-specific compound for the beetle *Hylecoetus dermesoides*, were accomplished.[102,103] Recently, an

Scheme 66



improved synthesis of 4-arylbut-2-enolides was realized using this approach giving access to 2-amino-substituted arylbutanolides which are potential precursors for naturally occurring aryl-substituted amino acids.[104] Other examples are the synthesis of monohydroxyeicosatetranoic acid (HETES) **262**,[105] coriolic acid (**263**),[106] 1,3-dimethyl-2,9-dioxabicyclo[3.3.1]-nonane (**264**), a host-specific substance for the ambrosia beetle,[107] homochiral 1,4-diols **265**,[108] and 2,5-disubstituted di- and tetrahydrofurans, e.g., **266**, Figure 5.[109,110]

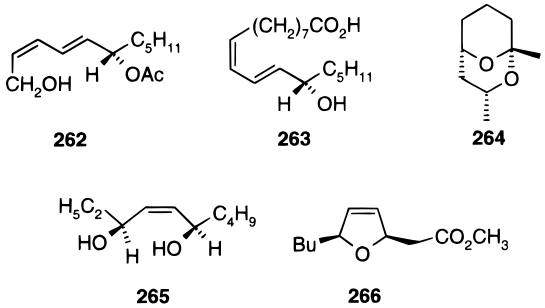
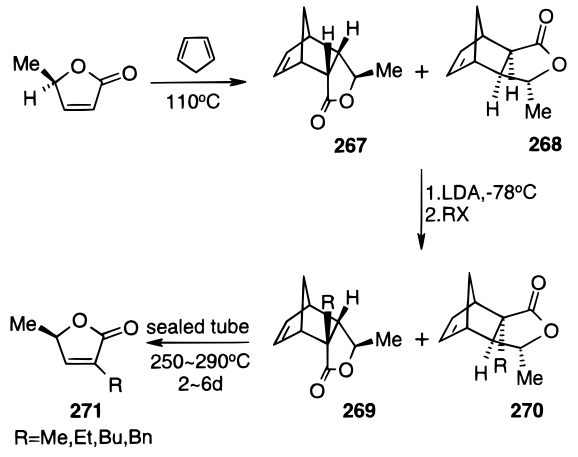


Figure 5.

Another although less practical route to optically active tricyclic lactones constitutes the asymmetric Diels−Alder reaction of (*R*)-angelica lactone with cyclopentadiene to enantiomerically pure *endo* and *exo* adducts **267** and **268** (Scheme 67).[111] Alkylation

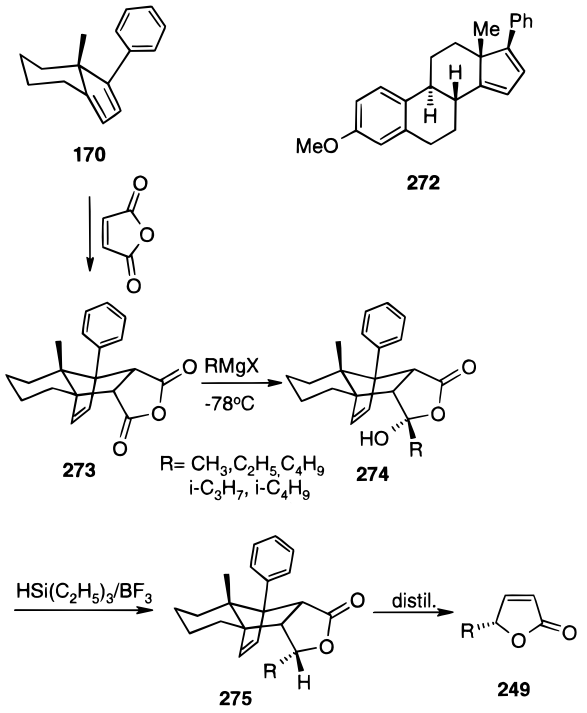
Scheme 67



of both diastereomeric adducts and subsequent cycloreversion provide an entry to optically active (*R*)-3-alkyl-5-methyl-2(5*H*)-furanones **271**. Interestingly, both alkylated diastereomers **269** and **270** produce the same butenolide **271**, illustrating that the production of a mixture of diastereomers in the initial Diels−Alder reaction need not necessarily be a serious problem when applying the concept of transient chirality in an enantioselective synthesis.

Winterfeldt's homochiral cyclopentadiene **170** and its steroid analogue **272** gave access to both enantiomers of butenolides **249** (Scheme 68).[112] Addition of

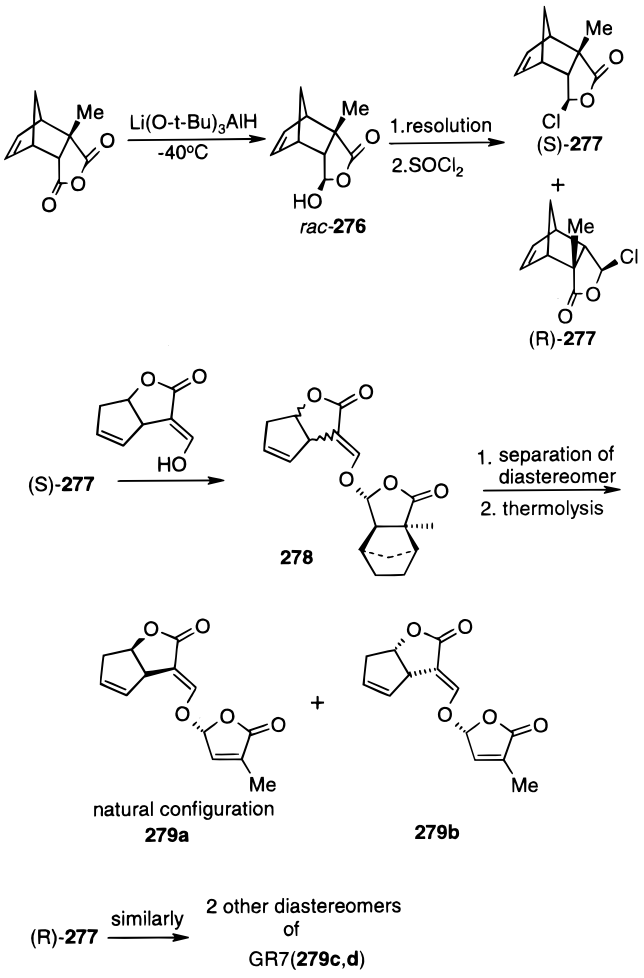
Scheme 68



Grignard reagents to bicyclic anhydride **273** proceeded stereoselectively to give lactol **274**, which on silane reduction produced lactone **275** with an acceptable stereoselectivity. Distillation from a Kugelrohr apparatus gave the desired butenolides **249**. The maleic anhydride adduct of **272** gave the other antipode because of the reversed stereochemistry in the organometallic addition reaction.[112]

An interesting application of transient chirality is the asymmetric synthesis of all four stereoisomers of the germination stimulant strigol analogue GR7 **279** needed for biological testing (Scheme 69).[113] Starting from the Diels−Alder adduct of citraconic acid anhydride and cyclopentadiene, *rac*-lactol **276** was obtained by partial lithium aluminum hydride reduction. Resolution of **276** with *l*-menthol gave both antipodes. Subsequent halogenation with thionyl chloride produced both (*R*)- and (*S*)-*exo*-chloride **277**, either of which was stereoselectively coupled with a racemic mixture of the appropriate enol to give **278**, which then was separated by chromatography to give both diastereomers in pure form. Thermal cycloreversion of either diastereomer of **278** by refluxing in *o*-dichlorobenzene produced the enantiopure diastereoisomers of GR7 **279a** and **279b**, respectively.

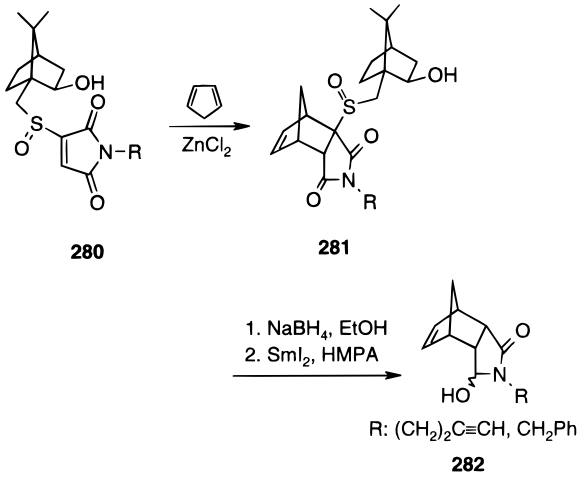
Scheme 69



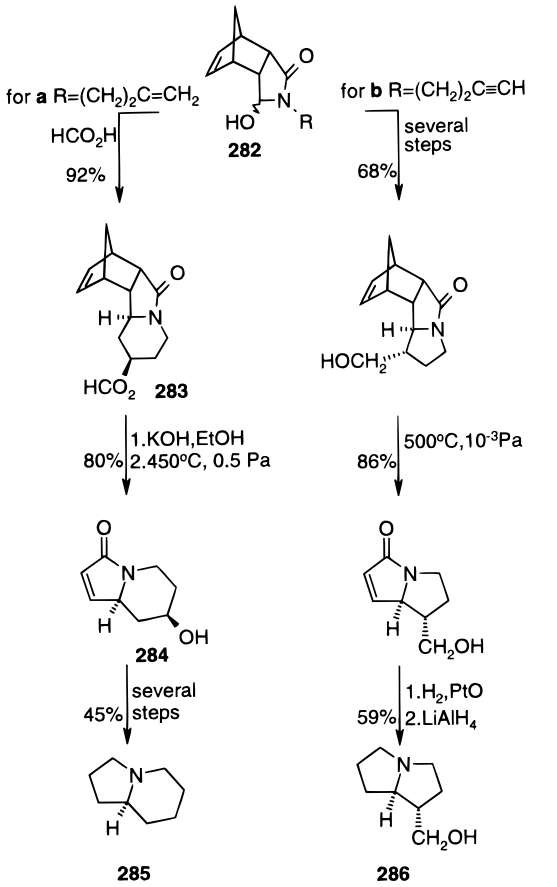
Starting from the (*R*)-diastereomer of **277** produced the other two diastereomers of GR7. An efficient kinetic resolution of racemic tricyclic hydroxylactones **276** was accomplished in a later stage of this study by lipase PS-mediated acetylation.[114] By employing this enzymic methodology, both enantiomers of *exo*-chloro lactones **277** could be obtained much more efficiently.

Intra- and intermolecular nucleophilic additions of acyliminium ions are an excellent method for the synthesis of nitrogen-containing natural products.[115] To achieve a high diastereoselective acyliminocyclization, Koizumi et al. synthesized optically active tricyclic lactam **282** taking advantage of the steric and chiral implications of the bicyclo[2.2.1]heptene moiety (Scheme 70).[116] Chiral lactam **282** was prepared from enantiopure maleimide **280**, which reacted with cyclopentadiene to give **281** in 96% *de*. Regioselective hydride reduction of **281**, followed by desulfinylation, gave **282** as a diastereomeric mixture (mixture of α- and β-C_5 alcohols). Starting from lactam **282**, the synthesis of a series of bicyclic alkaloids has been achieved (Scheme 71). Key steps in these syntheses involve diastereoselective addition to an acyliminium ion generated from **282** and the retro-Diels−Alder reaction. The synthesis of (+)-indolizidine **285** was accomplished using alkene **282a** (R = $(CH_2)_2C{=}CH_2$).[116] Acyliminium cyclization of **282a** using formic acid gave formate **283** as the only

Scheme 70



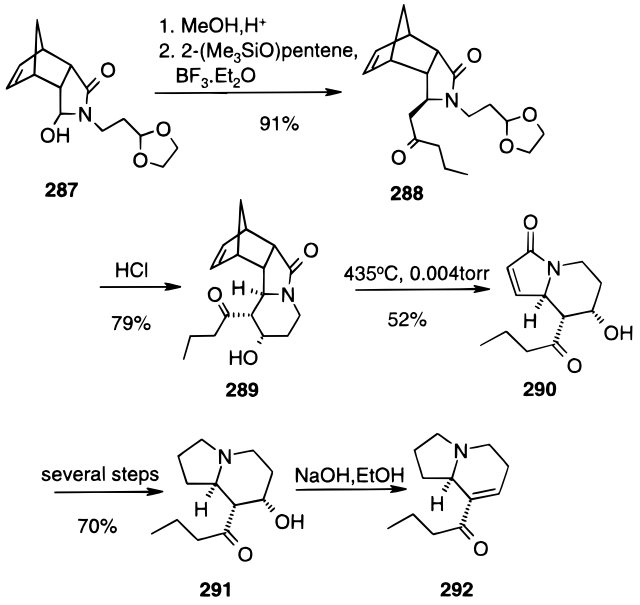
Scheme 71



product in excellent yield. Hydrolysis of **283**, followed by flash vacuum pyrolysis at 450 °C and 0.5 Pa, gave bicyclic alcohol **284** in 80% yield. Reduction of the double bond and removal of the alcohol function afforded the natural product **285** in good overall yield. Enantiopure (+)-laburnine (**286**) was synthesized using essentially the same procedure starting from alkyne **282b**.

An asymmetric synthesis of Elaeocarpus alkaloids (+)-elaeokanine A (**292**) and (+)-elaeokanine C (**291**) was accomplished by intermolecular addition of 2-(trimethylsilyloxy)-pent-1-ene in the presence of BF_3−etherate to give the bicyclic acyliminium ion derived from **287** to produce **288** (Scheme 72).[117]

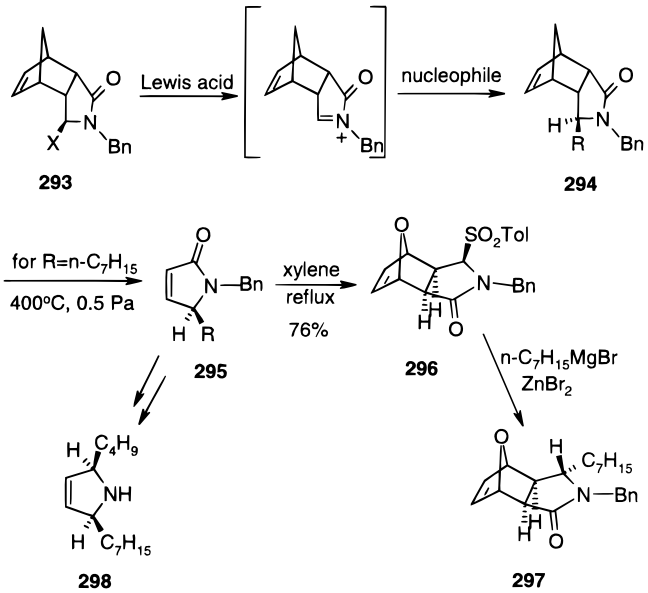
Scheme 72



Subjecting **288** to intramolecular aldol condensation under acidic conditions afforded the tetracyclic lactam **289**. Cycloreversion of **289** using flash vacuum thermolysis at 435 °C and 0.004 Torr gave a mixture of two pyrrolidinones in a ratio of 3:1 in high yield. The major product **290** (52% yield) could readily be separated. Reduction of the double bond and removal of the ring carbonyl function afforded (+)-elaeokanine C (**291**). Its unsaturated analogue, (+)-elaeokanine A (**292**), was readily obtained by dehydration of **291** under alkaline conditions.

N-Benzyl-substituted lactams **293** were applied for the synthesis of enantiopure 5-substituted 3-pyrrolin-2-ones **295** (Scheme 73).[118] Generation of the acylimin-

Scheme 73

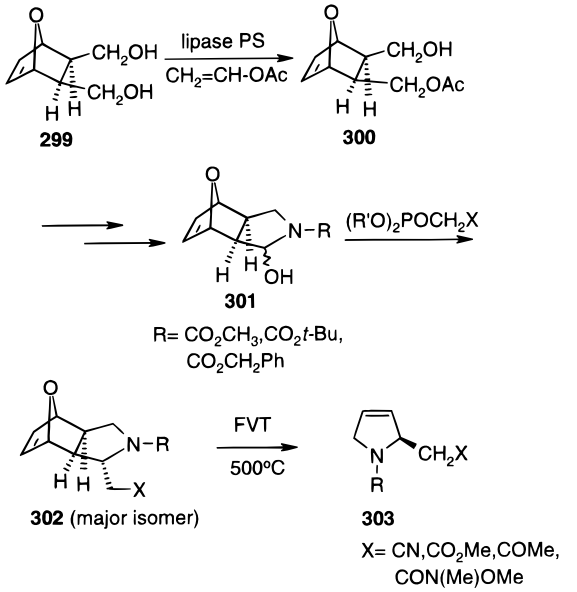


ium ion in the presence of appropriate nucleophiles, such allyltrimethylsilane and alkyl copper reagents gave exclusively the *exo*-5-substituted alkyl lactams **294** in a completely stereoselective addition reaction. By subjecting these lactams **294** to flash vacuum

thermolysis, acceptable yields of the corresponding pyrrolinones **295** were obtained (for R = *n*-C_7H_{15}, 76%) but the ee was moderate (for R = C_7H_{15}, 74% ee). To lower the temperature for cycloreversion to avoid possible thermal epimerization at C_5, the corresponding oxalactam **296** was prepared and used in this sequence (Scheme 73). Addition to the acyliminium ion derived from **296** was again completely stereoselective and took place from the less-hindered *endo* face to give **297**. Cycloreversion of **297** was already complete after 2.5 h in refluxing xylene (160 °C) to give enantiopure **295** (R = C_7H_{15}) in 71% yield. This (+)-pyrrolinone was used for the synthesis of cyclic amine **298**, which is a potent vasodilator.

Analogous to the synthesis of 2-substituted 2,5-dihydrofurans **258** (Scheme 66), Bloch prepared optically active 2-substituted 3-pyrrolines **303** from the hemiaminals **301** (Scheme 74).[119] The preparation

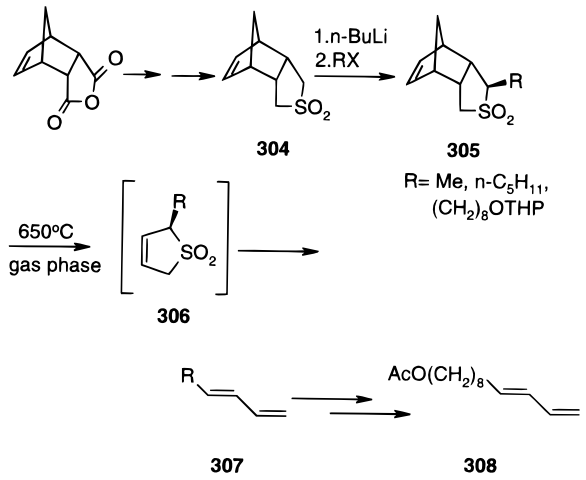
Scheme 74



of the key compounds **300** started with *meso*-diol **299**, which upon enzymatic acetylation using the lipase of *Pseudomonas cepacia* gave monoacetate **300** in 75% yield. From this acetate all the desired hemiaminals **301** were prepared applying the appropriate substitution reactions. Reaction of homochiral **301** with the anion of various stabilized phosphonates in THF under reflux gave the tricyclic *exo*-substituted pyrrolidines **302** in good to excellent yields and with good diastereoselectivity. Cycloreversion of **302** was carried out under flash vacuum thermolysis conditions at 500 °C to afford the 3-pyrrolines **303** in good yields and of high optical purity.

An interesting application of transient chirality, although not leading to chiral compounds, is the use of tricyclic sulfones **304** for the stereoselective synthesis of conjugated dienes **307** (Scheme 75).[120] Deprotonation of **304** with *n*-butyllithium in tetrahydrofuran leads stereoselectively to α-alkyl sulfones **305**, which on cycloreversion at 650 °C in the gas phase led to dienes **307**. The sulfolenes **306**, which are the initially formed cycloreversion products,

Scheme 75



cannot be isolated or detected. Under thermal conditions, they rapidly undergo sulfur dioxide extrusion in a chelatropic reaction to give dienes **307** in which the original stereochemistry of the alkyl group is translated in a specific geometric configuration. An application is the synthesis of (E)-9,11-dodecadien-1-yl acetate **308**, which is a component of the sex pheromone of the red-bollworm moth. In a similar way, a variety of (*E*,*E*)-1,4-disubstituted 1,3-dienes including some sex pheromones have been prepared by α,α′-bisalkylation of tricyclic sulfone **304**.[121] Other applications are the stereoselective synthesis of hypotensive vasodilator WS-1228 A (**309**)[122] and the naturally occurring conjugated dienamides pellitorine (**310**) and pipercide (**311**), Figure 6.[123]

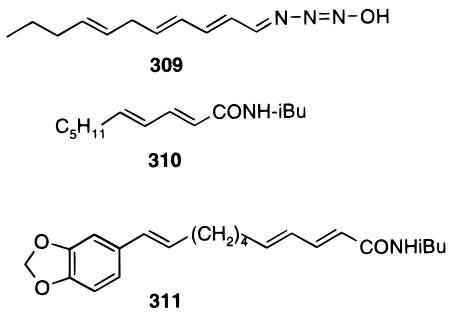
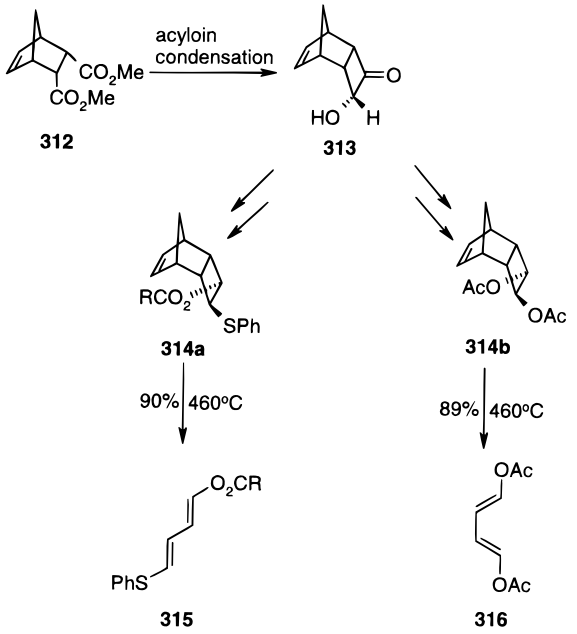


Figure 6.

A stereocontrolled synthesis of a variety of oxygen- and sulfur-substituted dienes has also been realized by cycloreversion of substituted tricyclo[4.2.1.$0^{2,5}$]-nonenes **314** (Scheme 76).[124] Starting from *endo*-diester **312**, acyloin condensation readily gave *endo*-α-hydroxycyclobutanone **313**. By appropriate functional group manipulation, stereocontrolled introduction of a variety of substituents at the C_3 and C_4 positions in the tricyclic system has been achieved. Examples are **315** and **316**. Gas-phase thermolysis of both compounds **314** at 460 °C gave the corresponding cyclobutenes, which however under these thermal conditions undergo concerted ring opening to produce stereoselectively the substituted dienes **315** or **316**. Again, the original stereochemistry of the substituents in the original tricyclic butane structure is reflected in the geometry of the produced dienes.

Scheme 76



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