Strategies for the Synthesis of Cyclic Ethers of Marine Natural Products

Tomás Martín,a,b Juan I. Padrón,a,b Víctor S. Martín*a

a Instituto Universitario de Bio-Orgánica ‘Antonio González’, Departamento de Química Orgánica, Universidad de La Laguna, C/Astrofísico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Spain
Fax +34(922)318571; E-mail: vmartin@ull.es

b Instituto de Productos Naturales y Agrobiología, CSIC, C/Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain

Received: 31.07.2013; Accepted after revision: 24.09.2013

Abstract: This account describes our studies on the synthesis of natural products that contain cyclic ethers in their structures. An overview of the main methodologies is presented and several total syntheses developed by the group are described. We also discuss new applications based on the use of Prins and Nicolas reactions as key steps in the preparation of oxygenated heterocyclic compounds.

1 Introduction
1.1 Natural Sources and Biogenesis
2 Carbon–Oxygen Bond-Formation Approach
2.1 Intramolecular Opening of Epoxy Alcohols and Related Bromo Cyclizations
2.2 Intramolecular Hetero-Michael Reaction of Alkoxy γ-Benzoyloxy α,β-Unsaturated Esters
2.3 Intramolecular Nicholas Reaction
3 Ring-Closing Metathesis of Unsaturated Linear Ethers
4 Prins Cyclization Promoted by Iron(III) salts
4.1 General Strategy
4.2 Cyclization Using Alkynols and the Formation of Vinyl Halides
4.3 The Use of Trimethylsilyl and Electron-Withdrawing Substituents in the Synthesis of 2,6-Disubstituted Tetrahydropyrans
4.4 Catalytic Prins Cyclization
4.5 Synthesis of Oxepanes
5 Summary

Key words: ethers, heterocycles, natural products, total synthesis, cyclization, ring closure

1 Introduction

Polyfunctionalized cyclic ethers are the structural keystones of a wide range of biologically active natural products, including polyether antibiotics,1 ladder marine toxins,2 annonaceous acetogenins,3 and lauroxanes4 (Figure 1). Many synthetic chemists have made extensive studies on the development of new strategies and efficient methodologies for the construction of ether ring systems and their applications in total syntheses of natural polymeric cyclic ethers. A number of excellent reviews on synthetic aspects of naturally occurring cyclic ethers have been published.5

In the development of methodologies for constructing cyclic ethers, three major approaches have been adopted; these involve (a) final C–O bond formation using a nucleophilic oxygen, (b) C–C bond formation in a preconstructed linear ether, or (c) simultaneous C–O and C–C bond formation in a single step (Scheme 1).

Figure 1 Examples of natural products containing cyclic ethers in their structures

Scheme 1 Main strategies for the synthesis of cyclic ethers: (a) C–O bond formation, (b) C–C bond formation, and (c) simultaneous C–O and C–C bond formation

Approach (a) is usually based on attack by a nucleophilic oxygen (generally a hydroxy or epoxy group) on an activated functional group (an epoxide, a leaving group on a saturated carbon, or an electrophilically activated alkene).6 The synthesis of cyclic ethers from lactones can be considered to fall within this category.7 Methods based on C–C bond formation [approach (b)] involve the formation of an acyclic ether that undergoes subsequent cyclization. Reactions such as ring-closing metathesis (RCM)8 or samarium-based coupling of aldehydes with suitable electrophilic alkenes have been applied to this end.9a Finally, the possibility of creating the oxygenated ring system by a process involving the formation of both a C–O bond and
a C–C bond [Approach (c)] is highly desirable. Among processes of this type, those based on the Prins cyclization have attracted a great deal of attention.9

With the aim of develop methodologies for the synthesis of bioactive natural products, especially those of marine origin, we have explored all three approaches outlined above. An overview of our researches in the synthesis of cyclic ethers is presented in this account.

1.1 Natural Sources and Biogenesis

Because of our interest in the natural products described in this account, we will summarize some of the most representative examples of biogenesis. As we will see, these biogenetic ideas have often been a source of inspiration for the development of methodologies used in syntheses of various natural products.

Red and brown algae are very important sources of marine natural products that exhibit a wide range of biological properties, including antitumor, antimicrobial, immunosuppressant, antifeedant, and pesticidal activities.10 Red algae of the genus Laurencia produce many unique compounds, including a series of nonterpenoidal C_{16}-metabolites, generally named lauroxanes, derived from metabolism of C_{16} fatty acids (acetogenins).10 For example, linear compounds, such as the enantiomers \((3E,9Z,12E)\)-pentadeca-3,9,12-trien-1-yne-6,7-diol [\(\text{trans-laurediol, } (E)\)-6] and \((3Z,9Z,12E)\)-pentadeca-3,9,12-trien-

Biographical Sketches

Tomás Martín received his B.Sc. in chemistry from the University of La Laguna, Tenerife, Spain in 1991, and obtained his Ph.D. in 1996 from the same university, working on the enantioselective synthesis of \(\gamma\)-lactones under the guidance of Dr. C. M. Rodríguez and Professor Víctor S. Martín. He was a postdoctoral fellow of the Spanish Ministry of Education and Science (MEC) at the Scripps Research Institute from January 1997 to December 1998, working on molecular recognition under the supervision of Professor Julius Rebek. In 1999, he returned to the Canary Islands, with a reincorporation contract of the Spanish MEC, and joined Victor S. Martín’s group. In 2002, he won a contract on the Ramón y Cajal program, created to boost Spanish science. In 2005, he became a tenured scientist at the Instituto de Productos Naturales y Agrobiología-CSIC. His research interests include supramolecular chemistry, methodology, and total synthesis of bioactive natural products.

Juan I. Padrón received his B.Sc. in chemistry from the University of La Laguna, Tenerife, Spain in 1990, and obtained his Ph.D. in organic chemistry in 1995 from the same university, working on the synthesis and stereochemical studies of saccharides under the guidance of Professor Jesús Trujillo Vázquez. He then spent two years (1996–1997) at the University of Columbia as a postdoctoral fellow with Professor Samuel J. Danishefsky, working on natural product synthesis. In 1998, he returned to the Canary Islands, and joined the laboratory of Professor Jaime Bermejo (CSIC). In 2004, he won a contract under the Ramón y Cajal program, created to boost Spanish science, working with Victor S. Martín at the University of La Laguna. In 2008, he became a tenured scientist at the Instituto de Productos Naturales y Agrobiología-CSIC, Tenerife, Spain. His research interests include sustainable metal catalysis and new reaction methodologies and their applications to natural product synthesis.

Victor S. Martín was born in La Palma (Canary Islands), Spain, in 1953 and gained his Ph.D. degree at the University of La Laguna, Tenerife, in 1978 under the guidance of Professors Antonio González, Julio D. Martín, and Manuel Norte. From 1980 to 1982, he was a postdoctoral fellow with Professor K. Barry Sharpless at Stanford University and at the Massachusetts Institute of Technology. He moved to the University of La Laguna as an associate professor in 1984. In 1988, was promoted to scientific researcher of the CSIC of Spain. Since 1992, he has held a full professorial position at the University of La Laguna. His research interests include asymmetric synthesis, methodology, and total synthesis of bioactive natural products.
1-yne-6,7-diol [cis-lauredial, (Z)-6],\(^{11}\) and cyclic products such as trans-(−)-kumausyne (4) and trans-(+)-deacetyl- 
kumausyne (5) have been isolated from Laurencia nipponica.\(^{12}\) Lauroxanes all contain polysubstituted cyclic 
ether moieties with a defined substituent stereochemistry and a ring size ranging from five to nine atoms. These 
cyclic ethers are considered to originate biogenetically from 
laurediols (6) through intramolecular electrophilic cyclizations induced by the bromonium ion (Scheme 2). 
Biosynthesis studies performed by Murai and co-workers\(^{13}\) demonstrated that lactoperoxidase and bromoperoxidase 
(BPO) catalyze this bromocyclization.

On the other hand, (2S,3S,5R)-5-[(1R)-1-hydroxydec-9-en-1-yl]-2-pentyltetrahydrofur-an-3-ol (7)\(^{14}\) and 
(2S,3S,5S)-5-[(1S)-1-hydroxydec-9-en-1-yl]-2-pentyltetrahydrofur-an-3-ol (8)\(^{15}\) are C19-diols isolated from 
Notheia anomala, a member of the Notheiaceae family, a taxonomically unique brown alga found along the coasts 
of southern Australia. These tetrahydrofurans are believed to be biosynthesized through cyclization of the natural 
methylene-interrupted bisepoxides 9 and 10, respectively (Scheme 3).\(^{16}\) They are potent and selective inhibitors of 
the larval development of parasitic nematodes.\(^{14}\)

A group of halogenated triterpenoids with several levels of oxidation and various cyclic systems form an important 
class of natural products isolated from Laurencia. All known metabolites are squalene-derived noncarbocyclic 
polyethers formed from the corresponding squalene-derived polyepoxides (Scheme 4).\(^{17}\) We became particularly 
interested in the synthesis of teurilene (11) and thyrsiferyl (12) and its congeners. Teurilene (11) was isolated, along 
with thyrsiferyl (12) and its acetyl derivative thyrsiferyl 23-acetate (13), from the red alga L. obtusa.\(^{18}\) Despite 
of containing eight stereogenic centers and three tetrahydrofur-an rings in its structure, teurilene has a meso symmetry 
\((C_s)\) making it an achiral compound. Thyrsiferyl (12) was the first example of a marine squalene-derived polyether 
triterpenoid containing a dioxabicyclo[4.4.0]decane moi-
tremely toxic and are responsible for neurotoxic shellfish poisoning, diarrheic shellfish poisoning, ciguatera, and other illnesses. It is accepted that these ladder toxins might be biosynthesized through a polyepoxide cascade cyclization (Scheme 5).25

Scheme 5  Biogenesis of brevetoxin B by polyepoxide cyclization

Natural products that contain cyclic ethers are not exclusive to the marine environment. For instance, polyether ionophores are a large group of natural biologically active substances produced by *Streptomyces* species. They are lipid-soluble and can transport metal cations across cell membranes.1 Another very interesting group of cyclic ethers from terrestrial environments are the polyether annonaceous acetogenins.3,26 This group of substances are produced by ionophores, which are widely distributed in tropical and subtropical regions. The typical skeleton of these substances is generally characterized by an unbranched C32 or C34 fatty acid ending in a butenolide moiety. Structurally, the compounds can be monotetrahydrofurans, adjacent bistetrahydrofurans, nonadjacent bistetrahydrofurans, tertetrahydrofurans, adjacent tetrahydrofuran–tetrahydrofurans, nonadjacent tetrahydrofuran–tetrahydrofurans, monotetrahydrofurans, or exclusively γ-lactones. The compounds have attracted the attention of many research groups because of their interesting structural complexity and their important biological activities (anticancer, antiprotozoal, pesticide, immunosuppressive, and antifeedant properties).26 Biogenetically, the annonaceous acetogenins appear to be formed through the polyketide pathway. The tetrahydrofuran, tetrahydrofuran, and epoxide rings might arise from isolated double bonds that undergo epoxidation and cyclization (Scheme 6).27

Scheme 6  Glaucanetin, a representative annonaceous acetogenin, biosynthesized by polyepoxide cyclization

2  Carbon–Oxygen Bond-Formation Approach

This approach represents the tactic that most closely resembles the way that nature synthesizes cyclic ethers. We will start by examining those methods and their applica-

2.1 Intramolecular Opening of Epoxy Alcohols and Related Bromo Cyclizations

Within our program directed toward the stereoselective total synthesis of bioactive substances of marine origin,28 we focused our attention on metabolites 4, 5, 7, and 8, which contain highly functionalized tetrahydrofuran rings (Scheme 7). Essentially, our idea was to synthesize the tetrahydrofuran ring by an intramolecular opening of an epoxide or bromonium derivative available from a suitable alkene. We surmised that the necessary linear unsaturated precursors might be stereoselectively synthesized by Wittig-type reactions of the lactol 16; this, in turn, would be accessible from the key γ-lactone 17. Lactone 17 should, in turn, be obtained in both enantiomeric forms by asymmetric dihydroxylation of the β,γ-unsaturated ester 18.29

Scheme 7  Retrosynthetic analysis of marine tetrahydrofurans

The necessary β,γ-unsaturated esters 18 were synthesized from the corresponding aldehydes by a modified Knovenagel condensation with malonic acid in the presence of piperidine as catalyst under nonpolar conditions, as exem-
plified in Scheme 8.\textsuperscript{30} Sharpless asymmetric dihydroxyla-
tion with the appropriate AD-mix gave the chiral β-
hydroxy γ-lactone 17a. In this step, we simultaneously
achieved two important goals: first, we introduced the
correct stereochemistry at two stereocenters for the final
molecule, and secondly, by the lactonization, we differen-
tiated chemically between the two hydroxy groups. Pro-
tection of the free secondary alcohol gave 17b, which
underwent selective reduction with diisobutylaluminum
hydride to give the corresponding lactols, primed for sub-
sequent Wittig homologation. For the stereoselective syn-
thesis of the C<sub>19</sub>-diol, tetrahydrofurans 7 and 8, we
considered a biomimetic approach based on the cycliza-
tion of the enantiomerically enriched bisepoxides 9 and
10.\textsuperscript{31} However, this approach would involve stereoselective
synthesis of epoxides derived from Z-olefins which,
in general terms, is difficult to achieve.\textsuperscript{31,32} To overcome
this difficulty, we focused our attention on the terminal
2,3-epoxy alcohol 20, which has the correct stereochem-
istry and is easily available by a Katsuki–Sharpless asym-
metric epoxidation of the corresponding E-allylic alcohol
19, obtained by homologation of the protected β-hydroxy
γ-lactone 17b. This strategy has three major advantages.
First, the synthesis of the diastereoisomer 22 can be
achieved simply by changing the chiral auxiliary at the
asymmetric epoxidation step. Secondly, a concomitant
cyclization to the tetrahydrofuran ring occurs during the
epoxidation step. Thirdly, the application of two enantio-
selective reactions ensures that the final products have
high enantiomeric purities.\textsuperscript{33}

The existence of precedents relative to the total synthesis of
trans-kumausyne from dihydroxy tetrahydrofurans
similar to 23 prompted us to perform a short formal syn-
thesis of a lauroxane (Scheme 9).\textsuperscript{34} This started with
butane-1,4-diol. The application of a series of steps similar
to those used in the syntheses of 21 and 23 gave tetra-
hydrofurans 24 as a pure stereoisomer. Protection of the
1,2-diol functionality as a dimethylether followed by cleavage
of the benzyl ether and subsequent oxidation gave the corre-
sponding aldehyde, which, without purification, was treated
with the ylide derived from commercially available triphenyl-
[3-(trimethylsilyl)prop-2-yn-1-
yl]phosphonium bromide to give the trans-enzyme 25 as the
sole geometrical isomer. Removal of the silyl groups,
acetylation of the secondary alcohol, hydrolysis of the di-
methyl acetal, and oxidative cleavage of the dial gave the
aldehyde 26. Because this aldehyde had previously been
transformed into trans-(−)-kumausyne (4),\textsuperscript{34} our approach
constituted a new formal synthesis of this natural prod-
uct.\textsuperscript{35}

In view of the simplicity with which it is possible to obtain
vicinal diols stereoselectively, we considered that the
methodology described above might also be used for the
synthesis of laurediols 6 (Scheme 10). We started with the
protected lactone 17d, which we subjected to carbon ho-
mologation in both directions to give the desired frame-
work. Removal of the benzyl protecting group, oxidation
of the primary alcohol, and stereoselective Wittig reaction

\textbf{Scheme 8} Stereoselective synthesis of (+)-(25,35,55)-5-[(1R)-1-
hydroxydec-9-en-1-yl]-2-pentyltetrahydrofuran-3-ol (7) and
(+)-(25,35,55)-5-[(1S)-1-hydroxydec-9-en-1-yl]-2-pentyltetrahydrofu-
ran-3-ol (8)

\textbf{Scheme 9} Formal synthesis of trans-(−)-kumausyne (4)
provided the (Z)-olefin 27. To complete the synthesis, we reduced the γ-lactone with one equivalent of disobutylaluminum hydride, and submitted the resulting lactol to Wittig olefination with the ylide derived from commercially available triphenyl[3-(trimethylsilyl)prop-2-yn-1-yl]phosphonium bromide to give the trans-enzyme. Fluoride-induced cleavage of the silyl-protecting groups then gave trans-(+)-laurediol (trans-6). 36

We began our synthesis from the silyl-protected threo-1,2-epoxy-3-alcohol 29, readily available from the known enyne 28 (Scheme 13). 38 The silyl epoxy ether 29 was used as the central fragment for homologation of the chain in both directions. Thus, the double bond in 29 was cleaved with ozone under reductive conditions and the resulting aldehyde was submitted to the appropriate Wittig reaction to give diene 30 with excellent stereocontrol. The terminal epoxide was opened with the lithium salt of a protected propargylic alcohol to give the linear chain 31, in which all the hydroxy groups were chemically differentiated ready for the cyclization reaction. 39 When we treated a solution of alkyne 31 in dichloromethane with 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one as a source of bromonium ions, we obtained a 1:1 mixture of the tetrahydropyran protecting group.

Although the above reaction showed better stereoselectivity, we considered the possibility of improving this further by manipulating the stereochemistry of the silyl-protected carbinal. We therefore prepared the precursor 35 from the erythro-epoxy ether 34 by a similar sequence of reactions (Scheme 14). The bromocyclization step gave the desired syn-2,5-disubstituted tetrahydrofuran 36 with an enhanced selectivity of 5:1. The one-carbon homologation to the trans-enzyme was performed by Corey’s method. 40 Finally, inversion of the configuration of the secondary carbinal by a consecutive sequence of oxidation and reduction reactions gave trans-(+)-deacetylkumausyne (5). 31

**Scheme 10 Total synthesis of trans-(+)-laurediol**

For the synthesis of exo-bromotetrahydrofurans, we considered an approach that is formally similar to the biogenetic origin of this type of compound. 28c Basically, this involved the synthesis of the tetrahydrofuran ring by an electrophilic bromocyclization of a suitable linear precursor. Because laurediols are assumed to be biogenetic precursors of the whole series of compounds (see above), a quite logical extension of our work was the direct synthesis of lauroxanes by this type of reaction (Scheme 11). Thus, when we submitted trans-(+)-laurediol (trans-6) to a bromocyclization reaction with 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one, we obtained trans-(+)-deacetylkumausyne (5), albeit with poor stereoselectivity.37

**Scheme 11 Bromocyclization of trans-(+)-laurediol to form trans-(+)-deacetylkumausyne (5)**

The low stereoselectivity achieved in the cyclization step prompted us to study the factors that might influence the stereochemical course of the reaction. Such studies might have eventually led to an alternative approach to the synthesis of the natural compounds. We therefore planned a different approach to (−)-deacetylkumausyne (5) based on the retrosynthetic analysis outlined in Scheme 12. We attempted to achieve high convergence in the synthesis of the hydroxyalkene precursors, with the aim of scaling up the amount of final product that was produced.

© Georg Thieme Verlag Stuttgart · New York

Synlett 2014, 25, 12–32
2.2 Intramolecular Hetero-Michael Reaction of Alkoxy γ-Benzoyloxy α,β-Unsaturated Esters

Intramolecular cleavage of an epoxide by an internal oxygen nucleophile favors the smaller heterocycle as a result of the transition state in which the attacking oxygen and the breaking oxirane C–O bond are collinear (exo-opening). In most approaches for promoting the desired endo-cleavage directing groups must be covalently attached to the epoxides. Water can serve as a promoter of an endo-selective epoxide-opening cascade if a single templating tetrahydropyran moiety is appended to a chain of epoxides.

The intramolecular Michael addition of an oxygen atom to an α,β-unsaturated ester can be considered as an interesting alternative strategy for the synthesis of tetrahydropyran rings. We considered the possibility that the geometry of the double bond might play an important role in the transition state of this hetero-Michael addition. Such a synthetic approach can be considered as being based on the possible biogenetic route to some natural tetrahydropyran moieties. In this respect, it had been proposed that the geometry of a transition state in which the attacking oxygen and the carbonyl group of the α,β-unsaturated ester with the cation of the base is necessary to obtain a suitable transition-state model. The experimental results can be rationalized in terms of a model with a pre-chair conformation in which the chiral inductor located in the equatorial position approaches the α,β-unsaturated ester in the axial mode for the E-isomer and in the equatorial mode for the Z-geometry (Scheme 16).

Our research focused on the study of the effects of the stereochemistry of the chiral centers and the double-bond geometry on the cyclization of substituted chiral 7-hydroxy-4-benzoyloxy-2,3-unsaturated esters (Scheme 15). We began our studies with the linear models 39 and 40, which have a known absolute configuration of the secondary allylic center. Asymmetric induction was performed by means of the Katsuki–Sharpless asymmetric epoxidation of a suitable allylic alcohol obtained from butane-1,4-diol. The enantiomerically enriched epoxy alcohol 37 was regioselectively opened by using benzoic acid as a nucleophile and titanium tetraisopropoxide as an acidic catalyst to give the benzoyloxy diol with excellent regioselectivity (>100:1). Oxidative cleavage with sodium periodate gave the aldehyde 38, primed for Wittig homologation. Treatment of aldehyde 38 with the sodium salt of trimethyl phosphonoacetate gave the E-unsaturated ester with excellent E/Z selectivity (>20:1). Similarly, when aldehyde 38 was treated with the sodium salt of 2-(diphenoxymethoxy)-2-oxoethyl]phosphonate, we obtained the Z-ester almost exclusively (Z:E >20:1).

Cleavage of the tetrahydropyran protecting groups from the E- and Z-esters under standard acidic conditions gave the corresponding free alcohols 39 and 40, respectively. Cyclization of the E-alcohol 39 gave the cis-2,3-disubstituted tetrahydropyran 41, whereas Z-alcohol 40 gave the trans-analogue 42.

Scheme 14: Biomimetic total synthesis of trans-(+)-deacetylkumausyne (5)

Scheme 15: Effect of the double-bond geometry in O-hetero Michael cyclizations to give 2,3-disubstituted tetrahydropyrans

Scheme 16: Computational study of the O-hetero Michael cyclizations
When the formation of all 2,3,5,6-substituted tetrahydropyrans is considered, the stereochemistry at the C2 position of the ring can be predicted by applying an empirical rule. If the chiral inductor (G) is prevented from adopting an equatorial conformation by geometrical restrictions, the trans-2,3-difunctionalized tetrahydropyran is always obtained. In this case, well-known 1,3-allylic interactions might be the cause of the preferred approach, although a different mechanistic pathway is also possible in such cases.49

This method has proved to be excellent for obtaining substituted tetrahydropyrans with high stereochemical purities. Under kinetic control (low temperatures and stoichiometric amounts of a sodium or potassium base), the procedure is particularly efficient for the synthesis of ladder-fused rings (Scheme 18). Thus, by starting from compounds containing a ring with a well-defined stereochemistry at the carbon on which the nucleophilic hydroxy group was located, six (43–48) of the eight possible diastereoisomers (only one enantiomeric series was considered) were prepared by direct intramolecular hetero-Michael addition reactions. The remaining two diastereoisomers (49 and 50) were synthesized by simple chemical transformations of the corresponding diastereoisomers of suitable stereochemistry. It must be emphasized that the isomerization of 46 to 50 was performed under thermodynamic conditions (room temperature). In a similar manner, 44 and 47 were isomerized to 45 and 48, respectively.51

### 2.3 Intramolecular Nicholas Reaction

Although it might be possible to synthesize seven-membered cyclic ethers by an intramolecular O-hetero Michael reaction, the necessity for the precursors to contain certain structural features (such as a Z-double bond) limits the usefulness of this procedure.52 To overcome this restriction, we developed a general method for preparing medium-sized cyclic ethers (six to nine members) that involves the intramolecular attack by a hydroxy group located on a saturated chain onto a carbocation generated by acid treat-

Interestingly, we found that epoxides can also be used as efficient nucleophiles in the intramolecular version of the Nicholas reaction. Thus, intramolecular attack by the epoxide on the exo-cation 52, generated by acid treatment of complex 51, gave the corresponding polysubstituted cyclic ethers (five-, six-, or seven-membered series) in good yields (Scheme 20). The regioselectivity of the cyclization is affected by a number of factors, including the distance between the epoxide and the propargylic cation, the nature of the substituents, and the nature of the reaction conditions.
of the protecting group on the primary alcohol, and the re-
action conditions.\textsuperscript{55}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme20.png}
\caption{Intramolecular attack of epoxides on \textit{exo}-propargyl cations to give polysubstituted cyclic ethers}
\end{scheme}

In a case where competition between the formation of six-
or seven-membered rings was possible, a \textit{tert}-butyloxycar-
bonyl protecting group on the hydroxy group of the termi-
nal 2,3-epoxy alcohol ensured that the disubstituted tetrahydropyran 53 was obtained exclusively (Scheme 21).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme21.png}
\caption{Intramolecular Nicholas reaction leading to a disubsti-
tuted tetrahydropyran}
\end{scheme}

On the basis of this methodology, we performed a retro-
synthetic analysis of (+)-muconin (2), in which the tetra-
hydropyran ring 53 (R = H) would act as a scaffold (Scheme 22). We first disconnected the saturated chain from the terminal epoxide 54, bearing in mind the possi-
bility of introducing such an alkyl chain by nucleophilic opening of the terminal epoxide ring. The tetrahydrofuran ring might be formed through in situ regio- and stereose-
lective \textit{exo}-cyclization of a suitable epoxy alcohol, which, in turn, might be obtained by a Katsuki–Sharpless asymmetric epoxidation of the allyl alcohol 55.\textsuperscript{55} This compound could be synthesized by an allyl Grignard regioselective opening of epoxide 56 with further homol-
ogation and reduction. Epoxide 56 would be derived from 53 (R = H) through a simple sequence involving partial hydrogenation and stereoselective oxidation.

After diol protection of tetrahydropyran 53, the next step involved stereocontrolled introduction of a secondary al-
cohol adjacent to the tetrahydropyran ring (Scheme 23). We performed this transformation by a two-step se-
quence. Partial hydrogenation with Lindlar catalyst and a

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme22.png}
\caption{Retrosynthetic analysis of (+)-muconin (2)}
\end{scheme}

Sharpless asymmetric dihydroxylation gave diol 57. Se-
lective tosylation of the primary alcohol group and forma-
tion of the terminal epoxy group under basic conditions gave the terminal epoxide 56. This product was opened with an allyl Grignard reagent in the presence of copper(I) iodide. Application of the known osmium tetroxide/sodi-
um periodate protocol to cleave the double bonds, fol-
lowed by Wittig reaction, and reduction with diisobutylaluminum hydride gave the intermediate allylic alcohol 55. Cyclization of 55 by concomitant asymmetric epoxide formation and cleavage gave the \textit{anti}-tetrahydrofuran 58 as the sole stereoisomer. The terminal epoxide 54, obtained by a similar sequence to that outlined above, was regioselectively opened by using the suitable Gri-
gnard reagent in the presence of copper(I) iodide to give the secondary alcohol 59. This acetonide had previously been transformed into (+)-muconin (15),\textsuperscript{56} so our ap-
proach constituted a new formal synthesis of this natural product.\textsuperscript{57}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme23.png}
\caption{Formal synthesis of (+)-muconin (2)}
\end{scheme}

As mentioned earlier, polycyclic ether natural products are formed by a cascade cyclization of a polypeoxide backbone. Therefore, epoxide-opening cascades have been used as a valuable method for synthesizing this type of compound.\textsuperscript{58} The main drawback of using the polye-
pxide-opening strategy is lack of control in the activation of the appropriate epoxide.\textsuperscript{59} This affects the yield of the cascade process if more than two epoxide groups are in-
volved. Therefore, the development of mild reaction condi-
tions that permit selective activation of a polypeoxide chain is vital for guiding the cascade event in the correct direction.\textsuperscript{60}
Because of the mildness of our procedure, we surmised that the use of a Nicholas cation as a suitable trigger might guide the cyclization process in a polyepoxide chain to give a polycyclic ether in a single step. To test our hypothesis regarding the predictability of the cascade cyclization event, we first decided to test it in a system with two epoxide groups on a carbon chain (Scheme 24). If the process evolved as expected, that is, through *exo* cyclization, it should generate two of the three tetrahydrofuran rings of teurilene (11) in one step. However, if the cyclization occurred in an *endo* manner, rings B and C of the thyrsiferol (12) would be formed.

With the concept of bidirectional synthesis in mind, the diepoxide 61 was easily obtained from commercially available cycloocta-1,5-diene (Scheme 25). 61 Introduction of the tert-butoxycarbonyl protecting group broke the C₂ symmetry of compound 61 and generated a well-documented terminating nucleophile for acid-promoted cascades. 62 The primary alcohol was oxidized and homologated through a Wittig reaction to give the α,β-unsaturated aldehyde 62. Hydrogenation generated the saturated aldehyde, which was immediately coupled with (trimethylsilyl)ethyne anion. The resulting compound was treated with octacarbonyldicobalt to give the model molecule 63, primed for cascade cyclization.

With the bisepoxide 63 in hand, we explored various reaction conditions. We found that silica gel promoted the Nicholas reaction to give a mixture of bitetrahydrofurans 64 and 65 in good yields after two steps (Scheme 26). Basic treatment of bitetrahydrofurans 64 and 65 gave the cyclic carbonates 66 and 67, which conveniently crystallized, permitting X-ray analysis for confirmation of their structures and stereochemistry.

By employing the bidirectional strategy, the known diol 69 was synthesized in good yield in four steps (Scheme 28). 63 The diol 69 was monoprotected as a silyl ether, leaving the bis(homoallylic) alcohol ready for homologation. By using the protocol developed by our group, we obtained the α,β-unsaturated ester 70 in one step and excellent yield. 64 The ester group was reduced with aluminum hydride to give the corresponding allylic alcohol. The first chiral epoxide was generated by a Katsuki–Sharpless asymmetric epoxidation, and subsequent protection gave compound 71. The silyl group was removed under standard reaction conditions and the resulting alcohol was oxidized to the corresponding aldehyde, which was coupled with lithium (trimethylsilyl)acetylide to give the propargylic alcohol 72. Finally, the remaining epoxides were installed in one step by a Shi asymmetric epoxidation to give the polyepoxide 74.

The formation of the hexacarbonyl dicobalt complex from 74 proceeded smoothly to give the intermediate 68, which we submitted to the cyclization conditions (Scheme 29). As expected, the cyclization process provided the three tetrahydrofuran rings in excellent yield (75% after two steps). The cascade is high yielding, averaging 91% per epoxide. Although the cascade proceeded efficiently the reaction gave a 1:1 epimeric mixture of 75 and 76 at the

Scheme 24  Cascade cyclization triggered by a Nicholas reaction in a diepoxide model

Scheme 26  Synthesis of the bitetrahydrofurans 66 and 67

Scheme 25  Synthesis of the diepoxide 63
propargylic position. From a synthetic standpoint, the epimeric mixture does not represent a problem for the synthesis of 11, because the propargylic ether can be isomerized at a later stage in the synthetic route. The isomers 75 and 76 were treated under basic conditions to remove the trimethylsilyl group from the alkyne and the tert-butoxycarbonyl group from the primary alcohol. Hydration of the terminal alkyne then gave the methyl ketones 77 and 78. The undesired isomer 78 was converted into the desired isomer 77 by treatment with a base. Transformation of the carbonyl group into the corresponding alkene was achieved through a Wittig reaction. The C$_5$ symmetry of the target molecule was produced by a Sharpless asymmetric dihydroxylation with the AD-mix $\beta$, which gave the meso-tetraol 79 exclusively. The meso-tetraol 79 was bidirectionally converted into the diepoxide 80 in good yield by a two-step protocol. Finally, diepoxide 80 was cleaved with a Grignard reagent in the presence of copper(I) iodide to give the natural product teurilene (11) in excellent yield.66

3 Ring-Closing Metathesis of Unsaturated Linear Ethers

We were able to prepare six- to nine-membered cyclic ethers (Scheme 19; $R^1 = R^2 = R^3 = H$) by means of the intramolecular Nicholas reaction with an alcohol as a nucleophile (the C–O bond-formation strategy).67 Also, by using this methodology, we were able to obtain an oxane–oxepane system (Scheme 19; $R^1$–$R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{O}$; $R^3 = \text{H}$, OBn; $n = 2$). However, this methodology gave poor conversions and poor yields of isolated eight-membered cyclic ethers ($n = 3$) when $R^1 \neq \text{H}$ or $R^2 \neq \text{H}$. Moreover, to obtain fused eight-membered cyclic ethers, such as the oxane–oxocane system ($R^1$–$R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{O}$; $R^3 = \text{H}$, OBn; $n = 3$), we were able to prepare six- to nine-membered cyclic ethers (Scheme 19; $R^1 = R^2 = R^3 =$...
OBn; \(n = 3\)), we needed at least two geometric control elements: a ring and a Z-double bond in the linear chain.\(^{68}\) Taking into account this limitation, we considered the possibility of developing a new strategy based on an intermolecular Nicholas reaction (Scheme 30). Because the RCM reaction has become the most powerful method for preparing cyclic products, we surmised that the cyclic ethers might be formed through a tandem intermolecular Nicholas reaction/RCM (the C–C bond-formation strategy). There are two possible approaches to this tandem strategy; in the first, the alkylene hexacarbonyldicobalt-complexed moiety is located in an endo position with respect to the cyclic ether (path a), and in the second, it is located in an exo position (path b).

By applying the endo strategy (Scheme 30; path a), we were able to obtain the saturated ethers (+)-cis-lauthisan and (+)-cis-obtusan.\(^{69}\) Their structures represent the basic skeletons present in a number of naturally occurring non-terpenoidal eight- and nine-membered ring ethers (Scheme 31). The synthesis of the cobalt-complexed ethers 86 and 87 began with the cobalt complex of commercially available racemic pent-1-yn-3-ol. Intermolecular Nicholas reaction with suitable allylic and homoallylic alcohols gave the \(\alpha,\alpha'-\)disubstituted linear ethers 82 and 83, respectively, with almost no stereocontrol of the newly created stereocenter. With ethers 82 and 83 in hand, the preparation of the necessary dienes for the RCM step required only simple alkylation with allyl bromide. Because cyclization to form a medium-sized ring is impractical with a free alkyl as part of the ring, the presence of a cobalt metallic core in 84 and 85 was crucial for ring closure. Compounds 84 and 85 were therefore treated with octacarbonyldicobalt to give the cobalt complexes 86 and 87, respectively.

There are three major advantages to the use of the cobalt alkene complex in the RCM process. First, the presence of the cobalt complex should prevent the undesirable participation of the triple bond in the metathesis process.\(^{70}\) Secondly, bending\(^{71}\) of the acetylenic system as a result of the formation of the cobalt complex might overcome the unfavorable entropic and enthalpic factors associated with the formation of eight- and nine-membered rings (the final ring has an endocyclic triple bond). Thirdly, the hexacarbonyldicobalt–alkyne complex in the endo position can serve as a stereochemical control for a critical isomerization process in the final cyclic product. RCM was performed by using the second-generation Grubbs catalyst under conditions of high dilution (0.001 M) in refluxing dichloromethane to give the ethers 86 and 87 in excellent yields. Interestingly, at this point of the synthesis the two diastereoisomers of 86 and of 87 could be readily separated by column chromatography on silica gel. However, because the major isomers isolated were trans-86 and trans-87, we considered the possibility of performing isomerizations to give the cis-isomers, because these are usually more stable thermodynamically. Fortunately, the use of montmorillonite K-10 as an acid in the Nicholas reaction proved to be highly efficient in inducing the desired conversion.\(^{72}\) Thus, the original mixture evolved quantitatively to pleasing cis/trans ratios of 17:1 for the eight-membered ring 88 and 21:1 for the nine-membered ring 89. Reductive decomplexification efficiently gave the corresponding cyclodienes, although these were obtained as inseparable mixtures of stereoisomers at the newly created double bond. However, hydrogenation under standard conditions cleanly gave (+)-cis-lauthisan (90) and (+)-cis-obtusan (91), respectively (Scheme 31).

© Georg Thieme Verlag Stuttgart · New York

Syntlett 2014, 25, 12–32
However, we could not obtain seven-membered oxacycles by this \textit{endo} strategy. We therefore developed a powerful and highly convergent method based on the alternative \textit{exo} approach that permits a very short synthesis of seven-, eight-, or nine-membered cyclic ethers by a genuine tandem intermolecular Nicholas reaction/RCM (Scheme 32).\textsuperscript{73} Our study began with an exploration to determine a suitable position for the double bond in the \textit{R} \textit{2} group of the cobalt complex that would avoid undesirable intramolecular Nicholas reactions or elimination reactions. After some experimentation, we found that complex 92 was the most appropriate for carrying out the intermolecular Nicholas reactions. With allylic, homoallylic, or bishomoallylic alcohols as nucleophiles, this complex gave the corresponding doubly branched ethers in very good yields.

With the diene complexes 93, 94, and 95 in hand, we performed RCM reactions with the second-generation Grubbs catalyst (Scheme 32). Treatment of the diene cobalt-complexes with 30 mol\% of the catalyst in refluxing dichloromethane (0.001 M) cleanly gave the desired cyclic complexes 96 (\textit{cis/trans} = 1.0:1.1), 97 (\textit{cis/trans} = 1.1:1.0), and 98, respectively, in excellent yields. When montmorillonite K-10 was used as the acid, the original mixture evolved quantitatively to a \textit{cis/trans} ratio of 3.0:1.0 for the seven-membered ring 96, and a \textit{cis/trans} ratio of 5.7:1.0 for the eight-membered ring 97 (Scheme 33).

The last steps required to complete the synthesis of the basic skeletons present in a number of naturally occurring nonterpenoids were decocplexation of the hexacarbonyldicobalt complexes \textit{cis}-96 and \textit{cis}-97, cleavage of the trimethylsilyl group with tetrabutylammonium fluoride, and further catalytic hydrogenation to give the saturated oxacycles \textit{cis}-101 and \textit{(+)}-\textit{cis}-lauthisan (90) in excellent yields (Scheme 33).

Additionally, by using this strategy, we developed a formal synthesis of the enantiomer of the natural product (\textit{+})-laurencin (1).\textsuperscript{73} This compound is one of the most representative members of the group of lauroxanes, and was first isolated from the extracts of the red algae \textit{L. glandelifera} by Irie and co-workers in 1965.\textsuperscript{74} Our route to oxocanes seemed well suited for use in conjunction with a total synthesis of (\textit{+})-laurencin (1) developed by the Overman group.\textsuperscript{75} In this synthesis, the oxocene 102 is an advanced intermediate that is converted in eight steps into the enantiomerically pure (\textit{+})-laurencin (1) (Scheme 34). Synthesis of oxocene 102 would, therefore, represent a formal synthesis of the natural product. As shown in the retrosynthetic analysis in Scheme 34, we surmised that oxocene 102 might be obtained through a simple reactions sequence from the cobalt hexacarboxyl complex \textit{cis}-103. Alkyne complex \textit{cis}-103 should be accessible by the three key steps used in our methodology: isomerization of the mixture of diastereomers 103 mediated by montmorillonite K-10 to obtain mainly the \textit{cis}-isomer, RCM of the un-
saturated branched ether cobalt complex 104, and intermolecular Nicholas reaction with the alcohol 105 and the acetylenic cobalt complex 106. However, we were aware that the cobalt complex 106 was not an ideal substrate for the synthesis of cyclic ethers, because the intermolecular Nicholas reaction needed to be carried at −20 ºC to avoid the formation of an elimination product.

Completion of the formal synthesis from the alkyne–cobalt complex cis-103 (P = TBDDS) involved transformation of the terminal alkyne to an analogue of Overman’s allylic alcohol 111 (Scheme 36). Although compound 111 has a similar protecting group to that in Overman’s intermediate, and could, therefore, be used to complete the synthesis of the natural product, we decided to check the structure of this compound and to achieve a formal synthesis of (+)-laurencin by changing the protecting group on the secondary alcohol give intermediate 102.

4 Prins Cyclization Promoted by Iron(III) salts

4.1 General Strategy

This approach is based on a rapid and direct access to oxygenated ring systems through a Prins cyclization using iron(III) salts as promoters or catalysts. This methodology combines the formation of C–O and C–C bonds in an oxacycle ring in a single step and is complementary to the other methods described above. The cyclization is driven through an oxocarbenium ion intermediate that is generated directly from the corresponding unsaturated alcohol (Scheme 37).

© Georg Thieme Verlag Stuttgart · New York Synlett 2014, 25, 12–32
Previously, this cyclization had been promoted by using a strong acid in a stoichiometric amount with a mixed acetal as the starting material. The main strategy was based on the generation of a mixed acetal (α-acetoxy ether) from the corresponding homoallylic alcohol. Taking these precedent into accounts, we considered the possibility of directly coupling an unsaturated alcohol with an aldehyde with an iron(III) salt as promoter. This strategy would have the advantages of using a homoallylic or homopropargylic alcohol as the starting material, thereby avoiding the need to generate the mixed acetal, and of using an inexpensive, environmentally friendly, and stable Lewis acid.

### 4.2 Cyclization Using Alkynols and the Formation of Vinyl Halides

First, to check the catalytic behavior of iron(III) salts in the Prins cyclization, we examined the reaction of but-3-en-1-ol (112) with several aldehydes in the presence of iron(III) chloride or bromide as promoter. The cyclization proceeded satisfactorily with both Lewis acids, giving the corresponding cis-2-alkyl-4-halo-tetrahydropyrans 113 in good yields (Scheme 38). We then extended our studies to the alkyne Prins cyclization. In this case, we obtained the corresponding 2-alkyl-4-halo-5,6-dihydro-2H-pyrans 115 in good yields by using but-3-yn-1-ol (114) instead of but-3-en-1-ol (112).78

However, when pent-3-yn-1-ol was used, the corresponding tetrahydrofurans 117 (R1 = Me) were the major cyclic products from acetaldehyde (R2 = Me; tetrahydrofuran/tetrahydropropan 35:65; 80%). The structure of the alkyne therefore determines whether endo cyclization to a tetrahydropropan 116 or exo cyclization to a tetrahydrofuran 117 occurs.

In this alkyne Prins cyclization, we found that an unexpected halide exchange occurs with halogenated solvents (Scheme 40). Through density functional theory studies, we detected an interaction between a halogenated solvent (dibromomethane) and iron(III) chloride that leads to the formation of a complex with a weakened C–Br bond. The presence of the reactive vinyl cation promotes bromine abstraction from the dibromomethane. In the case of the secondary carbocation intermediate of the alkene Prins cyclization, the vinyl cation is insufficiently reactive to promote abstraction of the bromine, leading cleanly to the chlorotetrahydropyan as the sole product. From the synthetic point of view, it is clear that for each halide the corresponding halogenated solvent must be used.79
homopropargylic alcohol (Scheme 42). However, the treatment of pent-4-yn-2-ol with 3-methylbutanal in the presence of iron(III) chloride gave the unsaturated (E)-β-hydroxy ketone 119 and the (E)-α,β-unsaturated ketone 120 in 65% yield, without any trace of the expected Prins-type dihydropyran product.81

The addition of a secondary homopropargylic alcohol to an aldehyde promoted by an iron(III) halide generates the oxocarbenium ion 121, which can evolve to the Prins cyclization. With chloromethyl or cyanomethyl substituents the relative rates of ring opening versus alkyne Prins cyclization do not take place.

Surprisingly, the resulting halosilyl alkenes 124 proved to be very unreactive systems. For instance, all attempts to cleave the C–Si bond under standard conditions were unsuccessful. Fortunately, however, the trimethylsilyl group was satisfactorily cleaved by refluxing the silylated alkene in aqueous hydriodic acid for one week (Scheme 45). Despite the long reaction time, the corresponding desilylated dihydropyran 125 were obtained in excellent yields with complete retention of the cis configuration.

Because the incorporation of a trimethylsilyl group as a substituent in homopropargylic alcohols 123 favors their Prins cyclization by destabilizing the allenic cation 122, we reasoned that similar results might be obtained by introducing other types of substituent that destabilize the corresponding allene cation and, consequently, accelerate the Prins cyclization.83 We decided to study the effects of electron-withdrawing groups, such as chloro or nitrile groups located in the position α to the hydroxy group, on the relative rates of ring opening versus alkyne Prins cyclization. With chloromethyl or cyanomethyl substituents (R1 = CH2Cl or CH2CN) as electron-withdrawing groups and a bulky aldehyde, such as cyclohexanecarbaldehyde...
(R^3 = Cy), the corresponding cis-2,6-disubstituted dihydropyrans 125 (R^2 = H) were the main products (Scheme 46).84

Scheme 46  Alkyne Prins cyclization of homopropargylic alcohols with electron-withdrawing groups located in the position α to the hydroxy group

The relative stability of intermediate species involved in 2-oxonia-[3,3]-sigmatropic rearrangement (Scheme 43) is the key factor to consider, because this can favor the Prins cyclization or the corresponding domino process. Therefore, we performed density functional theory studies on simplified structures. The results of these calculations are summarized in the energy diagrams shown in Figure 2.

Figure 2  Effects of silyl substituents on the relative-energy profile in the formal 2-oxonia-[3,3]-rearrangement

The α-silane allenyl cation 128 is 5.7 kcal/mol less stable than the homopropargylic analogue 126, which indicates that the rearrangement is not favored, and the dihydropyran 127 is protected from ring opening by an activation energy of 1.7 kcal/mol. The rearrangement is an endothermic process, and is less favored than the reaction without silicon (133 to 132). Furthermore, replacement of the silane substituent by a trimethylsilyl group results in an even less favorable rearrangement of 129 to 131. This energy profile correlates very well with our proposed mechanism.

Scheme 47  Proposed mechanism for the silyl alkyne-Prins cyclization

Density functional theory calculations suggested that the trimethylsilyl group stabilizes the dihydropyranyl cations in the dihydropyranium cation 130, leading to more-uniform reorganization of the electronic density in the ring. The calculations also showed that the trimethylsilyl group does not have a direct effect on the formally positively charged carbon atom.84

To confirm that no racemization occurred during the cyclizations to the tetrasubstituted dihydropyrans, we treated alcohol (R)-134 with phenylacetaldehyde and iron(III) chloride. The resulting dihydropyran 135 showed a slightly reduced but still synthetically useful enantiomeric purity compared with the starting homopropargylic alcohol (R)-134 (Scheme 48).

Scheme 48  Cyclization of an enantiomerically enriched homopropargylic alcohol

4.4  Catalytic Prins Cyclization

Next, with the aim of achieving greater sustainability, we focused on the development of a catalytic Prins cyclization (Scheme 49). We made considerable efforts to replace stoichiometric methods by catalytic processes, the halide source being our first concern. Trimethylsilyl halides were chosen, based on precedents with indium salts.85 Catalytic systems obtained by combining readily available iron salts with trimethylsilyl halides are widely applicable and promote the formation of substituted six-membered oxacycles.86 The key finding for this protocol is that a catalytic effect is produced by a combination of a readily available and inexpensive iron source [FeX_3 or Fe(acac)_3] and a trimethylsilyl halide. This catalytic method also permits the construction of chloro, bromo, or iodo heterocycles by appropriate selection of the iron(III) source, the trimethylsilyl halide, and the solvent.
A tentative catalytic cycle is shown in Scheme 50. We reasoned that the catalytic cycle might be initiated through activation of the aldehyde by the iron salt. The activated aldehyde then reacts with the unsaturated nucleophilic species to give an acetal precursor. The high stability of the accumulating iron oxide counterpart and the fact that the iron salt is the sole source of halide provide a thermodynamic sink that drives the conversion, but requires the use of a stoichiometric or excess amount of the iron(III) salt. We therefore devised an indirect way to complete the catalytic cycle through ligand exchange between the iron complex and a chlorosilane to regenerate the iron(III) salt. We therefore reasoned that the catalytic cycle might be initiated through a dynamic sink that drives the conversion, but requires the use of a stoichiometric or excess amount of the iron(III) salt. We therefore devised an indirect way to complete the catalytic cycle through ligand exchange between the iron complex and a chlorosilane to regenerate the iron(III) salt.

Scheme 49 Catalytic Prins cyclization

Scheme 50 Plausible mechanism for the iron-catalyzed construction of oxacycles through the Prins cyclization

4.5 Synthesis of Oxepanes

Having gained experience with the Prins cyclization described above, we focused our attention on developing a direct synthesis of oxepanes, for which a few precedents are found in the literature.87,88 Our studies on the direct synthesis of oxepanes began with the Prins cyclization of pent-4-en-1-ol (136, R² = H) with 3-methylbutanal in dry dichloromethane in the presence of a stoichiometric amount of iron(III) chloride (Scheme 51). The desired all-cis-disubstituted oxepane 137 was obtained in 56% yield, together with 41% of the monosubstituted tetrahydrofuran 138 (Scheme 51).89 By using more-hindered aldehydes (R² = Cy, t-Bu), the corresponding oxepane 137 was obtained exclusively, with none of the corresponding tetrahydrofuran. When we tested the cyclization of secondary bishomoallylic alcohols (136, R¹ ≠ H) under the same conditions, we obtained the all-cis 2,4,7-trisubstituted oxepanes 137 as the major products. Again, with a hindered aldehyde such as pivalaldehyde, the corresponding oxepane 137 was formed exclusively in good yield (75%).89

Scheme 51 Prins cyclization of oxepanes using stoichiometric amounts of iron(III) chloride

The presence of the tetrahydrofuran derivatives 138 prompted us to use our previously described catalytic system of an iron(III) salt and trimethylsilyl chloride. The application of this catalytic system to the Prins cyclization gave oxepanes in good yields, with none of the corresponding tetrahydrofuran derivative 138 (Scheme 52). With bishomoallylic alcohols 136, iron(III) chloride or tris(acetylacetonate)iron catalyzed the cyclization to give, in both cases, a mixture of cis-2,7-dialkylexopanes 137 and 139, differing in the stereochemistry of the chlorine atom at C-4. The use of tris(acetylacetonate)iron produced better results with aldehydes bearing functional groups such as double bonds. It should be emphasized that the excellent yields obtained from functionalized aldehydes with both iron(III) sources provides a route to other functional groups. The Prins cyclization generally led to 50:40 mixtures of oxepanes 137 and 139, respectively, except when a bulky aldehyde was used. From a synthetic point of view, the absence of stereochemical control at the chlorine-substituted carbon is not a limitation for the effective synthesis of the oxepane ring, as the chlorine atom can be easily removed to give a single cis-2,7-disubstituted oxepane.

Scheme 52 Iron(III)/trimethylsilyl chloride-catalyzed direct synthesis of substituted oxepanes

On the basis of our experimental observations, we propose a mechanism involving the catalytic formation of the oxocarbenium ion 140. The tetrahydrofuran 138 might be generated from the bicycle 143 (Scheme 53). In the oxepane 139, the ether oxygen participates in a transannular cyclization by an S₈ mechanism as a result of the optimal spatial requirement for the chlorine atom (internal O–C–Cl angle 166.7°), leading to the bicycle 143. The attack of the chloro group on the carbon adjacent to the oxonium, with R² as substituent, leads to the thermodynamically more stable tetrahydrofuran 138. In the case of bulky substituents at this position (R² = Cy, t-Bu), this attack is unfavorable, and the presence of tetrahydrofuran 138 is not detected. However, in the oxepane 137, the transannular
cyclization is unfavorable, because the oxygen and chlorine (internal O–C–Cl angle 141.7°) does not meet the spatial requirement for formation of the bicyclic 141 and, therefore, the tetrahydrofuran 142.

![Scheme 53 Proposed mechanism for the synthesis of 2,7-disubstituted oxepanes catalyzed by iron(III)](image)

To validate our methodology, we concentrated our efforts on a total synthesis of (+)-isolaurepan with a Prins cyclization as the key step (Scheme 54). We planned this synthesis from the enantiomerically enriched bishomoallylic alcohol 145, containing a hexyl group, which was obtained in one step. Regioselective ring opening of the known epoxide (−)-144 with allylmagnesium bromide in the presence of copper(I) iodide gave the desired bishomoallylic alcohol 145 in 90% yield (>99 ee). Prins cyclization of 145 with butanal was performed under standard reaction conditions with tris(acetylacetonate)iron as the iron(III) source to give the desired oxepane in 95% yield, and, in 90% yield. A final dehalogenation step gave (+)-isolaurepan in 95% yield (>99 ee). Prins cyclization of 145 with butanal was performed under standard reaction conditions with tris(acetylacetonate)iron as the iron(III) source to give the desired oxepane 146 in 95% yield. A final dehalogenation step gave (+)-isolaurepan in 90% yield. Starting from the enantiomerically enriched epoxide 144, we accomplished the most efficient and the shortest reported total synthesis of (+)-isolaurepan with 77% overall yield.

5 Summary

Cyclic ether moieties are very important structural motifs in many biologically active natural products. In this account, we have described several approaches that our group has adopted in synthesizing polysubstituted cyclic ethers. We have paid a great deal of attention to the biosynthesis of many of these compounds as a source of inspiration for planning of their syntheses. Three main approaches have been adopted. These are based, respectively, on the formation of a C–O bond as the key step, the construction of the cyclic ether by an RCM reaction in a preconstructed linear ether, and the synthesis of the oxygenated heterocycle by concomitant C–O and C–C bond formation in a Prins cyclization.

References


Acknowledgment

This research was supported by the Spanish MINECO, co-financed by the European Regional Development Fund (ERDF) (CTQ2011-28417-C02-01/BUQ and CTQ2011-22653) and the IMBRAIN project (FP7-REGPOT-2012-CT2012-31637-IMBRAIN), which is funded under the Seventh Framework Programme (CAPACITIES). We acknowledge our co-workers who participated in this research program, and whose names appear in the reference section. The authors thank Dr. David Tejedor for helpful discussions.

Synlett 2014, 25, 12–32 © Georg Thieme Verlag Stuttgart · New York
(73) Ortega, N.; Martín, V. S.; Martín, T. Org. Chem. 2010, 75, 6660.