Applications of Menthol in Synthetic Chemistry

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Received October 24, 2006

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1. Introduction

In this article, we aim at demonstrating the potential uses, possibilities, and successful applications of (−)- and (+)-menthol and its most prevalent derivatives in preparative organic synthesis.

The most intriguing examples and industrial applications are highlighted with emphasis on more recent examples. An exhaustive coverage of all the work and aspects concerning menthol was not projected; therefore, the industrial synthesis of menthol itself,[1] its organoleptic properties,[2] menthol-scaffold derived auxiliaries,[3] and racemate resolution techniques involving menthol derivatives are not discussed in detail within the range of this article.

Menthol or *p*-menthan-3-ol is a cyclic sesquiterpene that exhibits three stereogenic centers and therefore exists in four diastereoisomers as depicted in Scheme 1.

(−)-Menthol is the isomer that occurs most widely in nature and therefore sometimes is referred to as "natural" menthol, albeit all other isomers are found in peppermint oils as well. It has a distinct peppermint odor and, as the only one out of those eight isomers, exhibits a cooling sensation on the human skin.

Some chemistry has been performed on the menthol-scaffold itself, for example Corey's synthesis of pseudopterosin A,[4] but the focus herein is put on the auxiliary-based approach. Therefore, the nine most frequently used menthol derivatives were selected and their applications in asymmetric synthesis are presented in the following.

2. Menthol-Derived Compounds

2.1. Menthyloxy-2-[5*H*]-furanone

2.1.1. Synthesis

This chiral building block is certainly among the most commonly applied starting materials in "menthol chemistry" due to its numerous conversion possibilities, which allow

10.1021/cr068409f CCC: $65.00
Published on Web 05/09/2007

Heiko Oertling was born in 1974 in Karlsruhe and studied chemistry at the Technical Universities of Dresden and Berlin. He received his Ph.D. in organic chemistry from the University of Stuttgart under the guidance of Professor J. Christoffers in 2003. Postdoctoral studies with Professor K. P. C. Vollhardt at the University of California at Berkeley followed, and currently he is working as a chemist for symrise in Holzminden. His research interests focus mainly on the design of new physiological cooling compounds.

Horst Surburg was born in 1949 and studied chemistry at the University of Kiel. He joined former Haarmann & Reimer GmbH in Holzminden in 1980 and started with the research on natural fragrant materials before specializing in the synthesis of aroma chemicals and cosmetic ingredients. For years he headed the synthesis department within the Corporate Research of symrise and is now Senior Vice President globally responsible for innovations in the Scent & Care Division.

Dr. Aurélia Reckziegel was born in 1965 near Venâncio Aires (Brazil) and studied chemistry at the University of Santa Maria (Rio Grande do Sul). In 1994, she relocated to the University of São Carlos (São Paulo), where she started her Ph.D. thesis in the group of Professor J. T. B. Ferreira. Until her graduation in 1998 she worked in the field of identification and synthesis of biologically active organic compounds, in which she continued as a postdoc at the University of Hamburg in the group of Professor W. Francke within a cooperative project comprising the identification of chemical messengers of social bees supported by the DAAD. Since 2000, she has worked as laboratory manager in the R & D department of symrise, focussing on the synthesis and development of aroma chemicals and cosmetic ingredients.

Heinz-Jürgen Bertram was born in 1958 in Northern Germany and studied chemistry at the University of Hannover. He received his Ph.D. in organic chemistry in 1987 under supervision of Professor E. Winterfeldt and joined Central Research at Bayer AG in Leverkusen the same year. In 1990 he moved to former Haarmann & Reimer GmbH in Holzminden where he held various positions and in 2006 was appointed President of the Flavor & Nutrition Division of symrise. Currently he is a member of the executive board and an elected member of the RIFM board of directors.

for Diels−Alder reactions, 1,4-conjugate additions, 1,3-dipolar cycloadditions, [2+2]-photochemical additions, diastereoselective bishydroxylation, and tandem-Michael-addition processes. To the best of our knowledge, menthyloxy furanone (**4**) surfaced first in 1981[5] and is easily accessible on a gram scale (see Scheme 2).[6] Remarkably, the initial impulse came from industrial researchers at Roussel Uclaf who outlined the use of **4** as a chiral analogue of maleic anhydride.

The reaction sequence starts with a singlet photooxygenation of furfural (**2**). Subsequent acetalization of the resulting hydroxyfuranone **3** with either (+)- or (−)-menthol affords a diastereomeric mixture of **4a** and **4b**, which can be epimerized under acidic conditions. Crystallization from petroleum ether yields the diastereomerically pure menthyloxy furanone **4a**. When the naturally occurring (−)-menthol is employed, the product **4a** exhibits the *R*-configuration at the acetal carbon (as demonstrated in Scheme 2). The *S*-configured product is obtained as a crystalline material when (+)-menthol is used. The whole procedure is well documented, and experimental details are carefully described in the literature.[6]

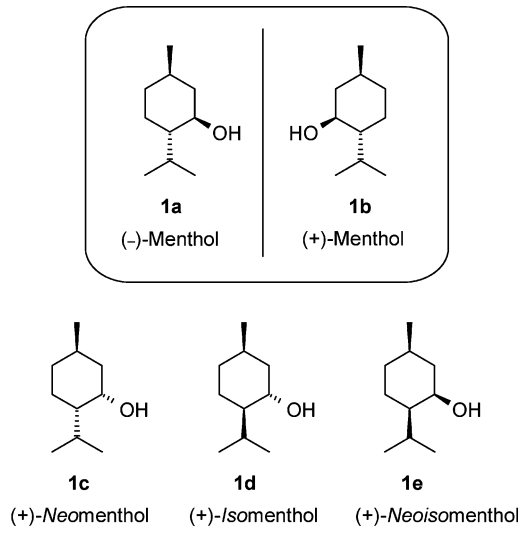
In this context, one should mention brominated derivatives of **4** and their resolution presented by Chen et al.[7] as well as the saturated lactone accessible via hydrogenation of the double bond moiety in **4**.[8]

2.1.2. Diels–Alder Reactions

Using chiral menthyloxy furanone **4** as a dienophile for Diels−Alder reactions is a reliable way of creating new stereogenic centers. Originally introduced by Feringa and co-workers,[9] this methodology applies to a variety of dienes **5** (see Scheme 3) and was recently used in Paquette's total synthesis of sclerophytin A.[10]

Conventional heating of Danishefsky's diene **5a** with menthyloxy furanone **4b** and subsequent cleavage of the silylenolether gave the *cis*-fused bicyclic framework **6** in

Scheme 1. Diastereoisomers of Menthol and One Enantiomer



good yield as the sole product. Compound **6** provided the basic scaffold for the synthesis of the respective cytotoxic soft coral metabolite.

A similar reaction protocol was applied in the synthesis of the tricylic system **7**. Starting from the 5(*R*)-configurated menthyloxy furanone **4a**, cycloaddition to cyclopentenyl silylenolether **5b** and adjacent hydrolysis resulted in one single stereoisomer **7**. One should acknowledge that four consecutive chiral centers were generated with excellent yield and selectivity. Employing non-functionalized hydrocarbon dienes **5c** and **5d**, the [4+2]-cycloaddition affords the corresponding products **8** and **9** in moderate to good yields.

Common in all these reactions is the strict π-face selectivity, which can be rationalized by the model depicted in Figure 1. As shown for cyclopentadiene (**5c**), only one of the four

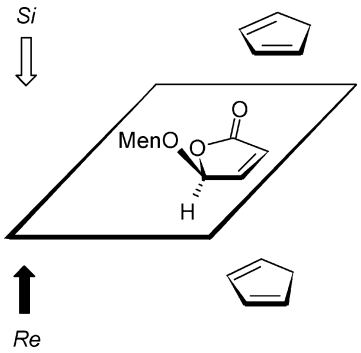


Figure 1. π-Face-selective Diels−Alder reaction of **4b**.[9]

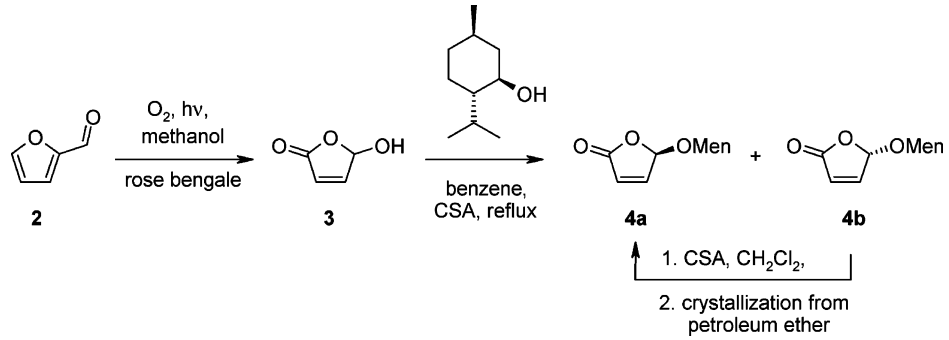
possible diastereoisomers is formed in the reaction with 5(*S*)-menthyloxy furanone **4b**, due to an *endo*-approach which takes place *anti* to the menthyloxy substituent.

In the case of **4b**, the sterically demanding menthyloxy group protects one side of the molecule from being attacked by cyclopentadiene, and a *Re*-face addition is expected for the 5(*S*)-menthyloxy furanone **4b**. Interestingly, furan does not react with **4** under various conditions.

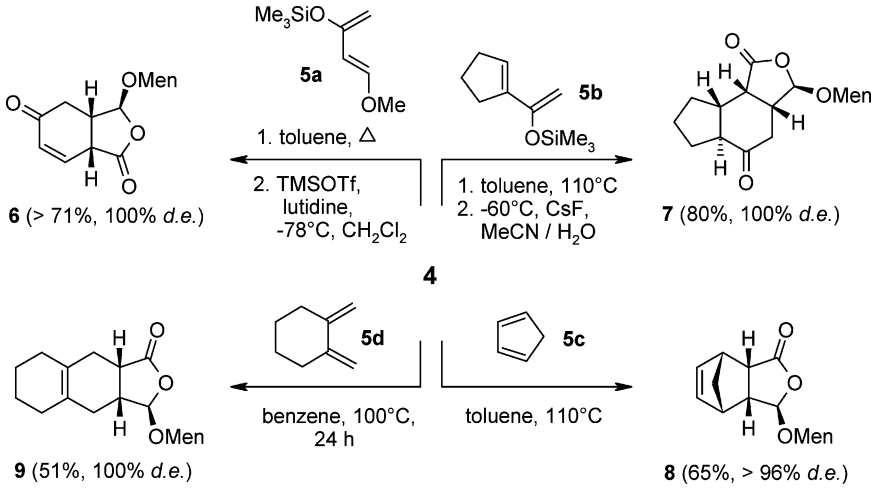
This Diels−Alder approach can be successfully intramolecularized, as was shown by Jauch (see Scheme 4).[11]

Starting from the substituted furanone **10**, which was derived from 5(*S*)-configurated menthyloxy furanone **4b**, the cyclization proceeds smoothly under strict exclusion of traces of acid (silylated flask), in order to avoid epimerization at the acetal center.

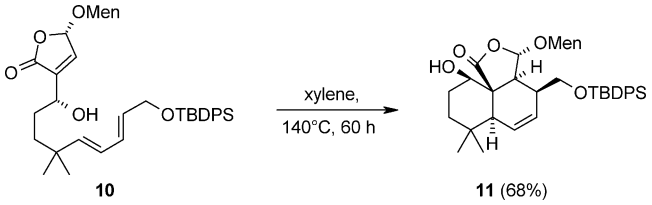
Scheme 2. Optimized Synthesis of Menthyloxy Furanone 4[6]



Scheme 3. Various Diels−Alder Products



Scheme 4. Synthesis of a Kuehneromycin A and Mniopetal Precursor According to Jauch[11]



10 **11** (68%)

Another example for this cycloaddition was presented by Bush and Jones[12] in 1996. The key step of their enantioselective synthesis of (−)-podophyllotoxin consists of an entirely regio- and stereoselective addition of 5(*R*)-menthyloxy furanone **4a** to pyrone **12** (see Scheme 5).

Again, the glassware in which the reaction was conducted was base-washed prior to use, but in this case due to the acid sensitivity of the generated tricyclic lactone. Subsequent cleavage of the latter in glacial acetic acid affords the podophyllotoxin carbon framework **13** in good yield.

2.1.3. Conjugate Additions

The standard organocopper addition of alkyl reagents seems to be difficult, and problems have been reported.[13] Usually conjugate addition to menthyloxy furanone **4** involves heteroatoms or heteroatom stabilized carbon nucleophiles. Nevertheless, one outstanding example was presented by Mulzer et al.[14]

In their efforts toward the synthesis of cobyric acid, the C-ring fragment **15** was prepared starting from menthyloxy furanone **4b**. Addition of vinyl Grignard reagent in the presence of copper(I) iodide afforded the desired lactone **14**. The reaction proceeded with almost complete stereoselection from the less hindered face due to the shielding effect of the menthyloxy substituent (see Scheme 6).

A similar example was presented more recently by Ishibashi et al. (see Scheme 7):[15] their synthesis of cyanobacterin, a photosynthesis inhibitor of freshwater cyanobacteria, commenced with the stereoselective addition of an isopropyl anion to menthyloxy furanone **4a**.

A subsequent second alkylation with dihalo compound **17** gave the alternating *all-trans* stereo-triad in **18** with good selectivity.

Michael Additions. The 1,4-addition of activated methylene compounds to menthyloxy furanone **4** was investigated by Kang et al.[16a,c] in 1997. Although few examples for Michael additions exist in the literature, simple conversion at room temperature in DMF catalyzed by NaOEt gives the diastereomerically pure products in high yields (see Scheme 8).

This selectivity is due to an attack from the sterically less strained face of **4a**. As ethyl cyanoacetate is a prochiral carbon nucleophile, it should be mentioned that the exocyclic stereocenter in **19d** is formed with a moderate selectivity of only 38% de.

Further intramolecular conversion of Michael products **20** was attained by Feringa et al.[16b] (see Scheme 9).

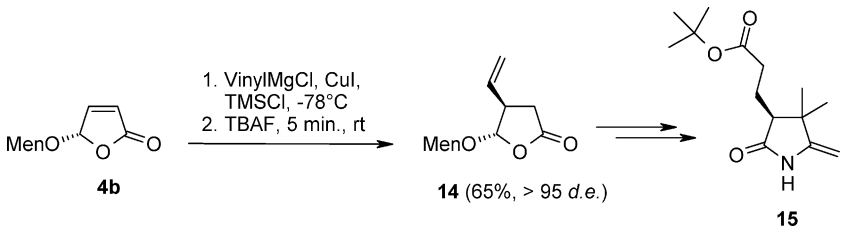
Exposure to $TiCl_4$ at low temperatures rearranges the carbon skeleton of **20** in a highly selective manner, and one single stereoisomer **21** is obtained.

Conjugate Tandem Addition of Sulfur-Stabilized Carbanions. Tandem reactions represent a very effective strategy to exploit the stereochemical information offered by a

Scheme 5. Diels−Alder Reaction of *o*-Quinonoid Pyrone 12

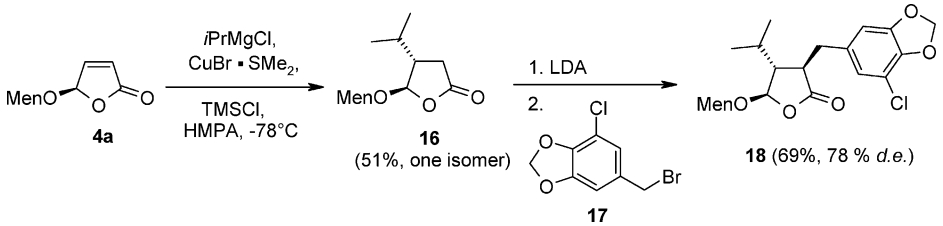
12 **4a** **13** (69%) only one diastereomer

Scheme 6. Synthesis of C-Ring Fragment of Cobyric Acid



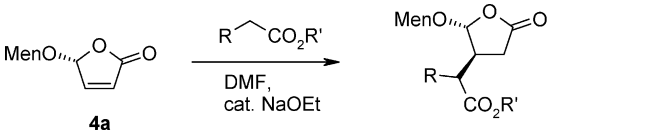
4b **14** (65%, > 95 *d.e.*) **15**

Scheme 7. Starting Sequence of the Cyanobacterin Synthesis by Ishibashi et al.[15]



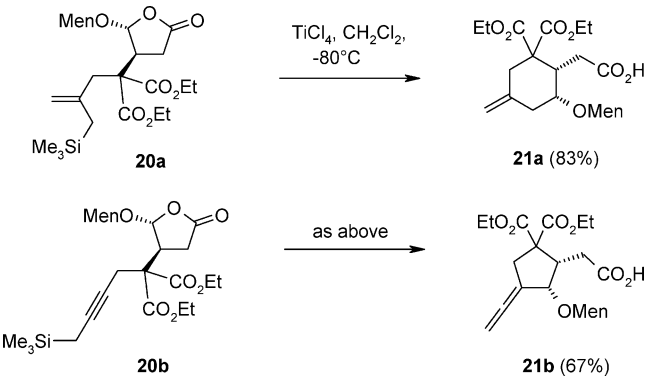
4a **16** (51%, one isomer) **17** **18** (69%, 78 % *d.e.*)

Scheme 8. Michael Addition According to Kang et al.[16a,c]

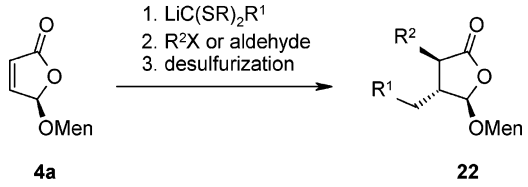


19a (R = NO_2, R' = Et, 92%),
19b (R = CO_2Me, R' = Me, 86%),
19c (R = CO_2Et, R' = Et, 70%),
19d (R = CN, R' = Et, 86%)

Scheme 9. Titanium-Mediated Sakurai-like Ring Opening−Ring Closure Sequence[16b]



Scheme 10. Synthesis of the *all-trans* Stereo-Triad via Tandem Addition (X = Hal)



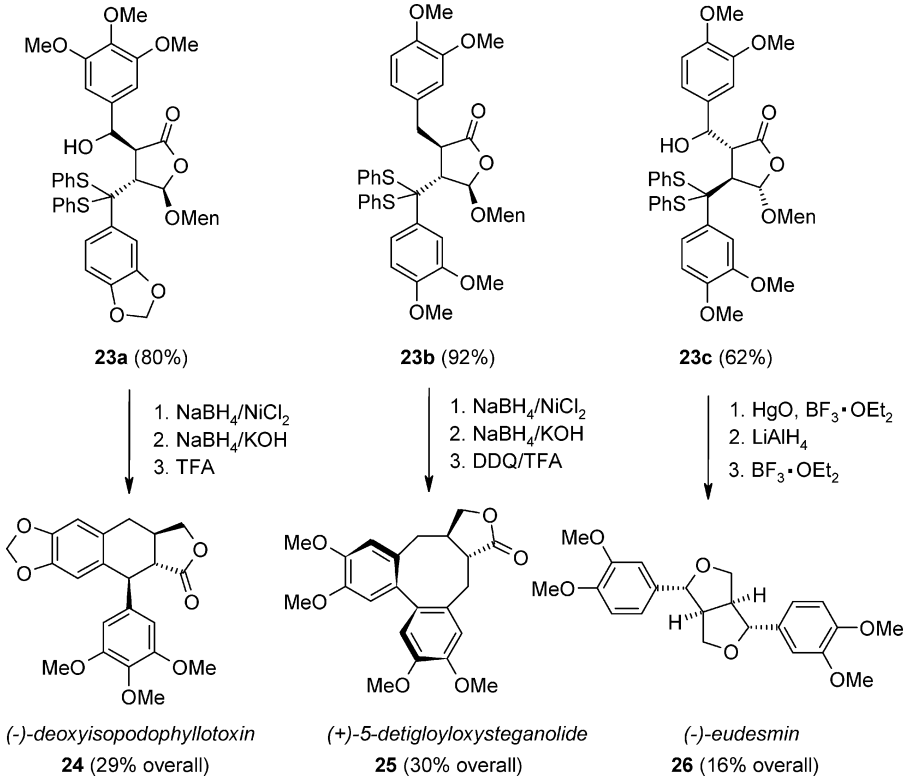
predefined stereocenter: the double bond in menthyloxy furanone **4** is readily attacked by sulfur-stabilized carbanions in a 1,4-fashion. The generated enolate anion can be trapped in situ by successive addition of a quenching agent, for example aldehydes or appropriate halogen compounds (see Scheme 10). The double addition takes place with complete stereoselection, and the *all-trans* relationship in **22** is established in a one-pot procedure. Hydrogenolytic cleavage of the sulfur appendices is accomplished by conversion with $NaBH_4/NiCl_2$ or Raney-nickel. The reliability and satisfying yields of this approach have led to the synthesis of a series of lignans, as is illustrated in Scheme 11.

The precursor scaffold to such different molecules as (−)-eudesmin (**26**),[17] (−)-deoxyisopodophyllotoxin (**24**),[18] and (+)-5-detigloyloxysteganolide (**25**)[18b] were menthyl derivatives **23**. Pelter, Ward et al. prepared **23a** and **23b** starting from 5(*R*)-configurated menthyloxy furanone **4a** in excellent yields. Subsequent desulfurization and adjacent dementholization lead to aryltetralin **24**; the final cyclization step is accomplished in neat trifluoroacetic acid with a yield of 92%. Biphenyl **25** was assembled in a similar fashion, although in this case the concluding step is an oxidative biaryl coupling. Remarkably, in the course of their synthesis, the rigid *trans*-lactone moiety of **23b** imposed its chirality on the newly formed biaryl unit in **25**.

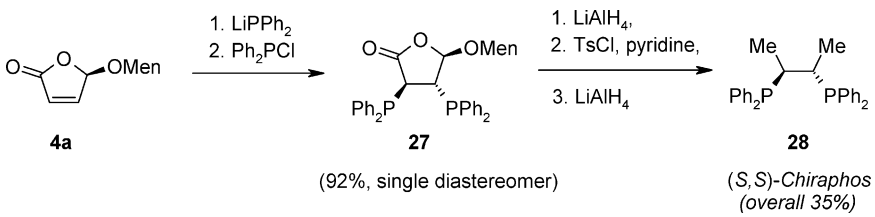
Utilizing the 5(*S*)-menthyloxy furanone **4b**, Feringa and co-workers obtained **23c** in 62% yield, which was then transformed into symmetrical lignan (−)-eudesmin (**26**) in an overall yield of 16%: dithiane **23c** was converted into the corresponding ketone using HgO in the presence of $BF_3{\cdot}OEt_2$. Subsequent multistep reduction with $LiAlH_4$ gave a tetrol, which was cyclized to the final product **26** by dehydration again using $BF_3{\cdot}OEt_2$.

Conjugate Addition of a Phosphorus Nucleophile. Feringa and co-workers[19] synthesized the enantiopure diphosphine **28** in a straightforward reaction sequence (see Scheme

Scheme 11. Enantioselective Syntheses of Different Lignans via Tandem Addition



Scheme 12. Synthesis of Enantiopure (*S,S*)-Chiraphos[19]



12). Again, menthyloxy furanone **4a** served as the readily accessible starting compound; addition of lithio diphenylphosphide at −90 °C and immediate trapping of the generated enolate with the corresponding chlorophosphine affords the *all-trans* lactone **27** as a single diastereoisomer.

Further conversion gave the desired ligand **28** in 35% overall yield. Of course, the (*R,R*)-enantiomer of **28** is amenable by switching the absolute configuration of the starting material **4**.

Conjugate Addition of *N*-Nucleophiles. Amines add readily to the double bond of menthyloxy furanone **4**, and this reaction was investigated in depth by Feringa and co-workers.[20] Simple stirring at room temperature gives the desired products **29** in moderate to excellent yields (see Table 1). The addition proceeds in a diastereoselective fashion, so that all β-amino lactones **29** obtained exhibit an isomeric purity of de > 92%. These substrates can be converted into optically active β-lactams **30**, which resemble useful precursors in the synthesis of carbapenem antibiotics, via an acid-catalyzed ring-opening, subsequent saponification, and concluding ring-closing lactamization (as indicated in Scheme 13).[20c]

Table 1. Addition of Several Amines to Menthyloxy Furanone 4 at Room Temperature

amine	solvent	reaction time (h)	yield (%)
pyrrolidine	CH_2Cl_2	0.5	76
piperidine	CH_2Cl_2	0.5	68
morpholine	DMF	1	73
diethylamine	DMF	2	95
n-butylamine	DMF	1	90
benzylamine	DMF	8	50

Since the 1,4-addition of amines to **4** is a reversible process, the purification of products **29** by distillation is inadvisable. Pure compounds **29** were gained by crystallization instead.

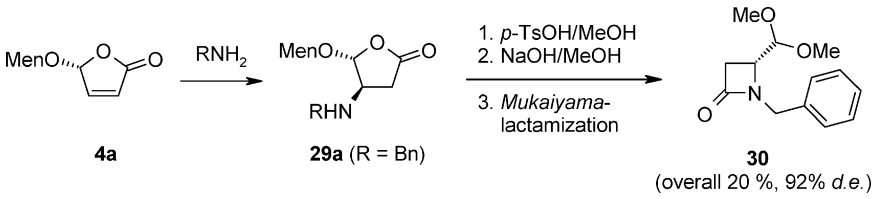
The solvent of choice in all these conversions was either DMF or dichloromethane, allowing short reaction times of 0.5−8 h.

Even two-fold reactions are easily accomplished: mixing piperazine and 5(*R*)-menthyloxy furanone **4a** in DMF in a 1:2 ratio results in instant formation of **31** as a crystalline solid (see Scheme 14).[21]

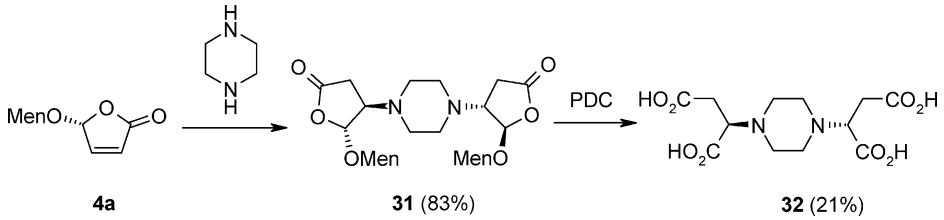
Subsequent oxidation with pyridinium dichromate gives enantiopure tetraacid **32**, which is capable of complexing europium ions in aqueous solution and is therefore feasible as a chiral shift reagent.

Recently, Chen and co-workers[22] reported on the synthesis of acyclic nucleoside analogues containing adenine (see Scheme 15). Direct addition of adenine in DMSO gave

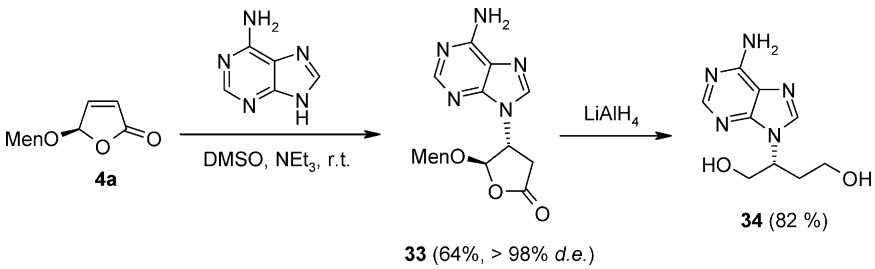
Scheme 13. Diastereoselective 1,4-Addition of Amines to Menthyloxy Furanone 4a



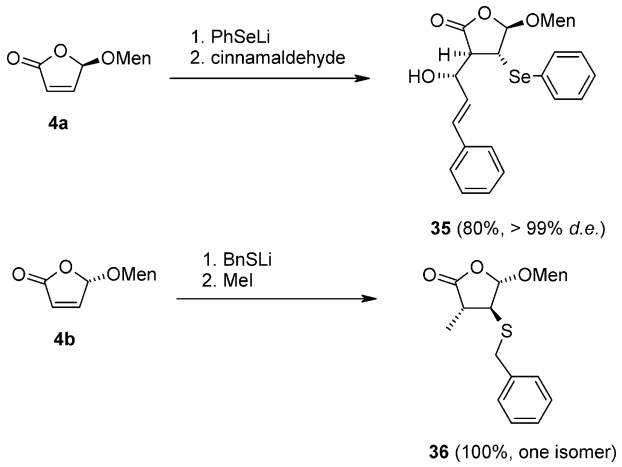
Scheme 14. Feringa's Synthesis of a Chiral Ligand for Europium Shift Reagents[21]



Scheme 15. Addition of Adenine to Menthyloxy Furanone 4a[22]



Scheme 16. Tandem Conjugate Addition Applying Sulfur and Selenium Nucleophiles



crystalline material **33** after chromatographic work-up in almost enantiopure form.

$LiAlH_4$ reduction affords the optically pure butanediole **34** in 82% yield, which can be cyclized via Mitsunobu methodology to the corresponding tetrahydrofuran derivative.

Conjugate Addition of Sulfur and Selenium Nucleophiles. Sulfur and selenium nucleophiles add easily in a 1,4-fashion to menthyloxy furanone **4**. In general, such additions are high-yielding processes, and the selectivities obtained are excellent (see Scheme 16). In analogy to Scheme 10, the generated enolate can be trapped by successive addition of either aldehyde or alkyl halides. In 2001, Jauch[23] applied this methodology successfully in his syntheses of a set of natural products.[11]

Addition of lithium phenylselenide and subsequent addition of cinnamaldehyde at −60 °C affords compound **35** in 80% yield with a selectivity of de > 99%. Strikingly, three new stereocenters are constructed in a one-pot reaction with perfect stereoselection.

A similar reaction sequence was applied by Feringa and co-workers[24] in their synthesis of chiral 1,4-butanols, which involves lithiated benzylthiol as a nucleophile and methyliodide as a quenching agent. Compound **36** was therefore obtained in quantitative yield as one stereoisomer. Nevertheless, this approach could not be generalized for different mercaptans or alkyl halides.

Finally, one should mention that the addition of oxygen nucleophiles to **4** has been described for primary alcohols by Kang et al. in yields ranging from 82 to 97%.[25]

2.1.4. Conversion to Chiral Cyclopentenones

Cyclopentenones are valuable synthons, particularly as enantiomerically pure building blocks. Most commonly acknowledged is their application in the synthesis of prostaglandins or jasmonates. Although at first glance they are not related to one another, chiral butanolide derivatives **37** can be conveniently converted into their cyclopentenyl analogues **38** (see Scheme 17).

Conversion of **37** with lithiated dimethyl methylphosphonate results in a ring-opening reaction under loss of the menthyl auxiliary and subsequent ring-closure via a Horner-Wadsworth-Emmons reaction. Scharf et al.[26] prepared **37b** from 5(*S*)-menthyloxy furanone **4b** in two steps on a 20 g scale: bishydroxylation with potassium permanganate (proceeding with complete diastereoselection) and acetalization gave the furanoside **37b** in 52% yield. Submission to the outlined procedure afforded cyclopentenone **38b** as an enantiomerically pure compound (ee > 99%).

Analogously, Robertson et al.[13] converted the *all-trans* bisalkyl furanone **37a** into enone **38a** with an unoptimized yield of 60%. Their synthesis commenced with a conjugate butylcopper addition to 5(*R*)-menthyloxy furanone **4a**. Introduction of the second alkyl substituent was achieved via a stereoselective prenylation of the lithium enolate in an overall yield of 33%.

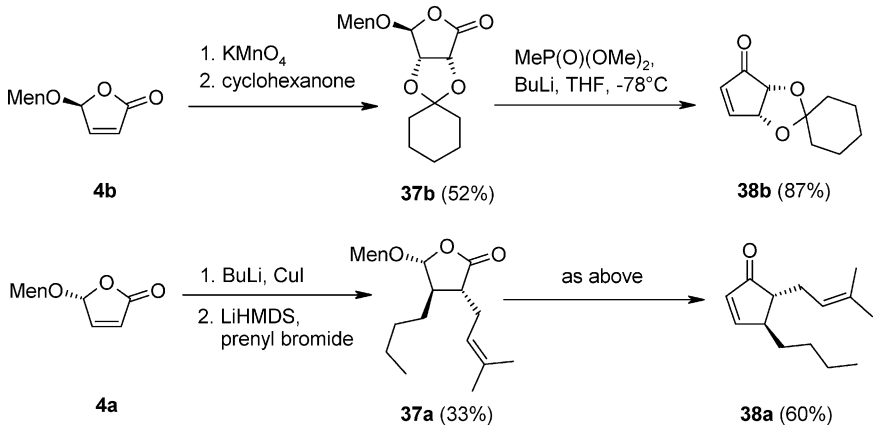
2.1.5. 1,3-Dipolar Cycloadditions

Use of 1,3-dipolar cycloadditions in organic synthesis is ubiquitous, mostly because in one step multiple stereocenters can be generated with high selectivities and usually good yields. This also applies for menthyloxy furanone **4** as it has been shown by Feringa et al.[27] (see Scheme 18).

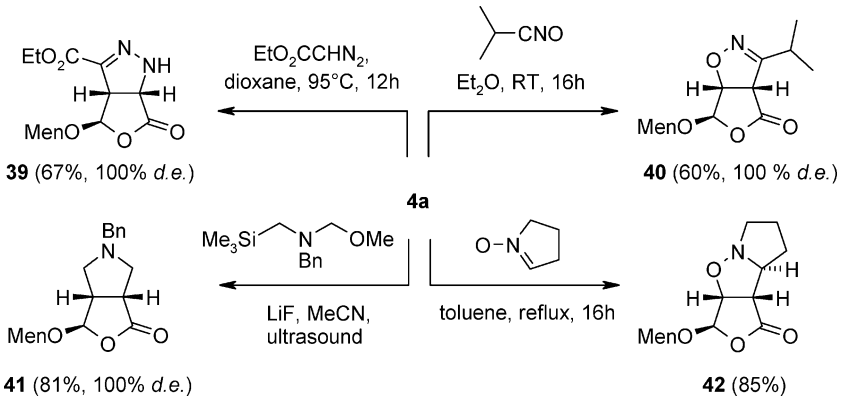
Chiral dipolarophile **4a** reacts smoothly with ethyl diazoacetate in dioxane to furnish solely compound **39** as a chiral pyrazoline derivative. Remarkably, the reaction proceeds with perfect regio- as well as diastereoselectivity, due to an *anti*-facial approach of the 1,3-dipolar reagent with respect to the alkoxy-substituent. Conversion of **4a** with in situ generated nitrile oxides gives isoxazoles in satisfying yields as mixtures of regioisomers: in the case of the isopropyl derivative **40**, a ratio of 92:8 was determined in favor of the depicted isomer in Scheme 18. It is noteworthy that again complete diastereoselectivity was achieved.

Switching to azomethine ylide additions, *cis*-bis-functionalized pyrrolidines are accessible: ultrasound-assisted generation of the corresponding 1,3-dipole gives diastereomerically pure *N*-protected bicycle **41**, again as a consequence

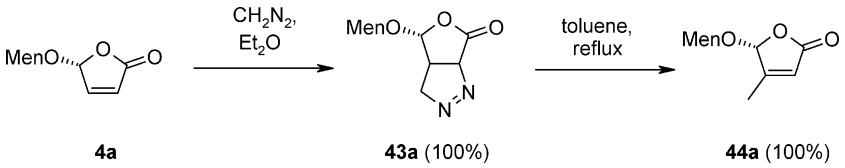
Scheme 17. Tandem Ring Opening/Intramolecular Horner-Wadsworth-Emmons Olefination



Scheme 18. Addition of Various 1,3-Dipoles to Menthyloxy Furanone by Feringa et al.[27]



Scheme 19. Synthesis of Enantiomerically Pure Methyl Furanone 44a According to Feringa[6c]

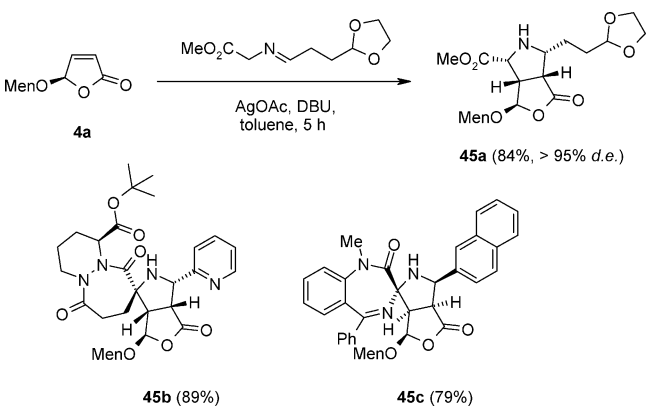


of the *anti*-facial approach. Steric congestion is responsible for an exclusive attack from the sterically less encumbered direction. Another example is the addition of dihydropyrrole oxide, which results in the formation of isoxazolidine **42**. Bridgehead stereocenters in **42** are constructed with perfect stereoselection due to the steric hindrance exerted by the menthol moiety in **4**. Nevertheless, no complete stereocontrol is gained over the third chiral center, and therefore cycloadduct **42** accumulates as a 7:1 mixture of two diastereoisomers. The major isomer **42** (as depicted in Scheme 18) arises from an *exo*-approach of the cyclic nitrone to menthyloxy furanone **4a.**

Addition of diazomethane gives pyrazoline **43** with exclusive regioselectivity but no stereoselectivity.[6c] Nevertheless, under refluxing toluene, extrusion of nitrogen occurred with an exceptionally good yield and afforded the methyl-substituted furanone **44a** in a convenient fashion (see Scheme 19).

Further examples for cycloadditions are presented by Grigg and co-workers.[28] Starting from the corresponding imines, the authors react (*R*)-menthyloxy furanone **4a** in the presence of DBU to receive complex cyclic systems **45** (see Scheme 20).

Scheme 20. Cycloaddition Products According to Grigg et al.[28]

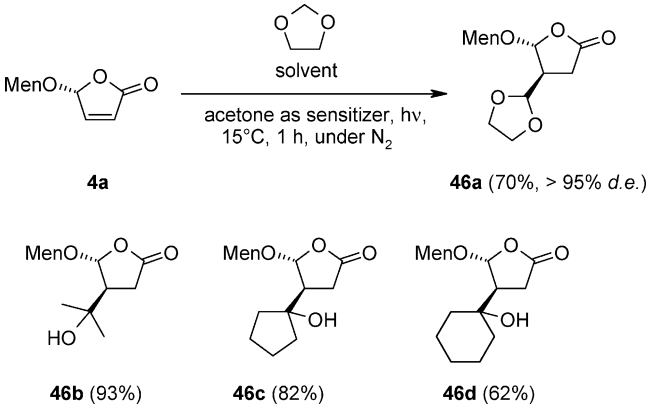


In the case of the non-spirocyclic system **45a**, four new stereocenters are introduced with a stereoselectivity of >95% de; analogously spirocyclic systems **45b** and **45c** are obtained as one stereoisomer in enantiopure form. The reaction proceeds under mild conditions at room temperature, and its generality was demonstrated for more than ten examples.[28a]

2.1.6. Radical Reactions

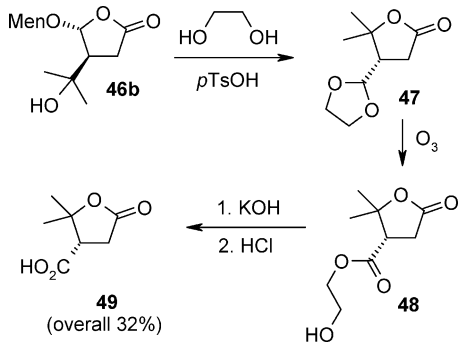
Although light-induced radical reactions are considered to suffer from the drawback of low selectivity, some impressively fruitful examples are introduced by Hoffmann.[29] In the presence of acetone as a sensitizer and the reagent alcohol as solvent, menthyloxy furanone **4a** is smoothly converted into products **46**. The reaction solution is irradiated for 1 h, and the generated radical adds in a 1,4-fashion to **4a**. The diastereoselectivity for all examples shown exceeds 95% de (see Scheme 21).

Scheme 21. Radical 1,4-Addition as Conducted by Hoffmann[29]



As demonstrated by the use of 1,3-dioxolane to furnish **46a**, this method is not limited to secondary alcohols. The preparative use of this approach is illustrated by a short synthesis of (−)-terebic acid (**49**) accomplished by Hoffmann (see Scheme 22).

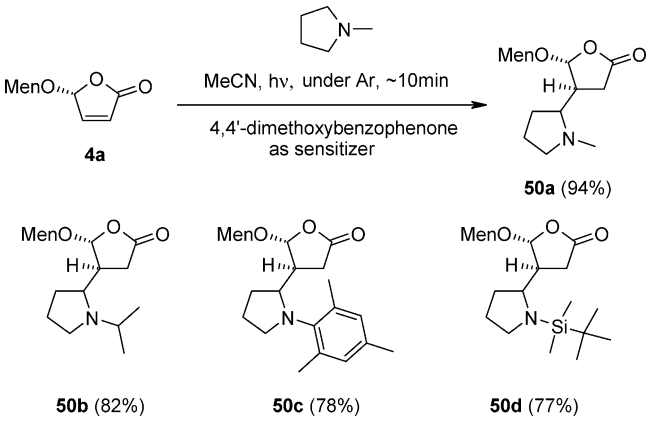
Scheme 22. Asymmetric Synthesis of (−)-Terebic Acid 49[29]



Treatment of tertiary alcohol **46b** with ethyleneglycol and *p*-TsOH affords the rearranged dimethylbutanolide **47**, which is subsequently reacted with ozone and after saponification yields the optically active acid **49**.

Irradiating tertiary amines derived from pyrrolidine in the presence of 4,4′-dimethoxybenzophenone as a sensitizer furnishes the respective 1,4-addition products **50** in good yields and with the expected facial selectivity.[30] No control is exerted on the second asymmetric center generated within this C−C-bond formation; therefore, all the products shown in Scheme 23 are received as mixtures of diastereoisomers.

Scheme 23. Addition of Aminoalkyl Radicals to 4a According to Hoffmann et al.[30]



As the steric bulk in the pyrrolidine derivative increased, the yields decreased and the ratio of diastereoisomers was shifted.

Employing this methodology, Hoffmann et al.[31] presented a concise synthesis of several necine bases, as shown in Scheme 24.

Starting from the diastereomerically pure addition product **50**, a reductive cleavage of the auxiliary followed by a photosensitized oxidative removal of the *N*-methyl group, subsequent intramolecular cyclization, and final alanate reduction yields (−)-isoretronecanol (**53a**) in 33% overall yield. The indolizidine scaffold **53e** could be synthesized in an analogous manner in 26% overall yield.

An extension of this versatile concept, namely, a radical tandem cyclization, leads to such diverse structures as tetrahydroquinoline **54**, benzoindolizidine **55**, or azasteroid **56** (see Scheme 25).[32,30b]

Generation of the nucleophilic dialkylaniline radicals proceeds via a photochemically induced electron transfer in the presence of Michler's ketone as sensitizer. Double addition of *N*,*N*-dimethyltolyl amine yields predominantly isomer **54**, accompanied by traces of the product where the attack took place from the sterically crowded furanone side. This also applies for the reaction with a tetrahydronaphthyl amine derivative, giving azasteroid scaffold **56** in satisfying yields. Switching to *N*-phenylpyrrolidine results in the formation of a diastereomeric mixture of **55**, for no stereocontrol is exerted on the chiral center in the α-position to the amine nitrogen. A stereomechanistic model is depicted in Figure 2 to illustrate the pathway leading to compound **54**.

Photochemically generated α-aminoalkyl radical **A** attacks menthoxy furanone **4a** in a π-face selective fashion. The next step comprises an intramolecular addition of the electrophilic oxoallyl radical **B** to the aromatic system, and the *cis*-fused stereochemistry of bicyclic intermediate **C** is established. A final rearomatization concludes this radical reaction sequence. Note that in the case of blocked *ortho*-positions in the phenyl ring tandem cyclizations could not be observed.

2.1.7. [2+2]-Cycloadditions

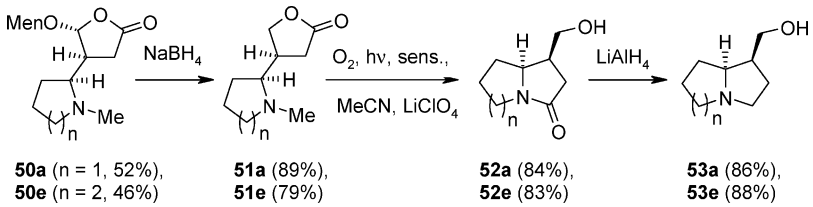
The most fundamental bimolecular [2+2]-cycloaddition utilizes ethylene as a participant, constructing a cyclobutane ring in a one-step fashion. Photochemically induced cyclization with enantiopure furanones **4b**, **44b**, or **57** gives the bicyclic system **58** in exceptionally good yields (see Scheme 26).[33] However, only low or almost no diastereoselectivity is obtained, irrespective of the adjacent substituent on the furanone ring.

Lowering the temperature results in higher selectivities, whereas the best result is achieved at −85 °C, albeit accompanied by a loss in chemical yield. Nevertheless, if the diastereomeric products are easy to separate, this reaction can be employed for the synthesis of optically active products; for example, **58b** has been separated from its diastereoisomer by chromatography on a 50 g scale.

Further conversion of **58b** (see Scheme 27) led to (+)-grandisol (**60**), a pheromone of the cotton boll weevil, in 34% overall yield. Starting from chloroderivative **58c**, the chiral diol **59** is accessible via cerium supported permethylation in 75% yield.

Cycloaddition of **4a** to cyclic enones has been reported on by Hoffmann et al.[34] Good results were obtained by employing isophorone as an enone: a mixture of four

Scheme 24. Asymmetric Synthesis of (−)-Isoretronecanol 53a[31]



Scheme 25. Radical Tandem Addition of Tertiary Amines[32,30b]

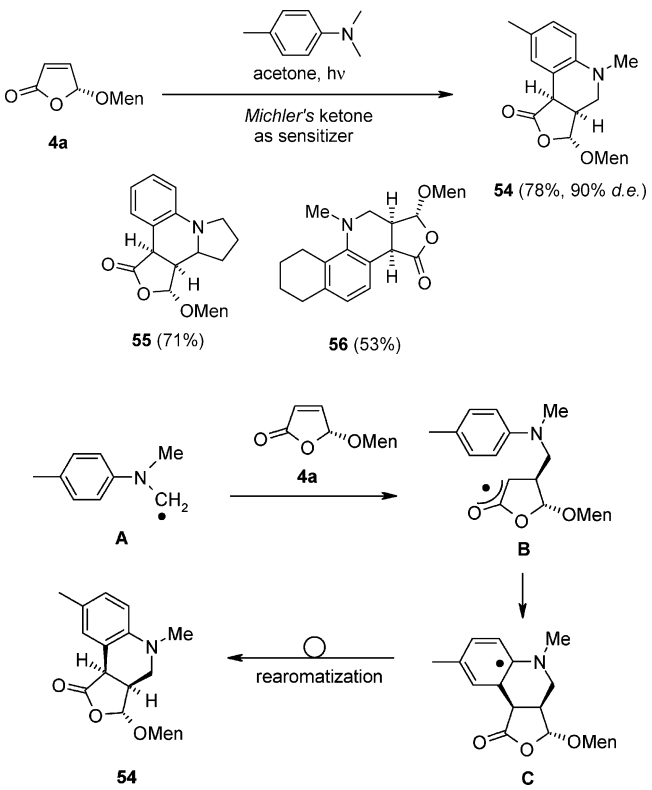
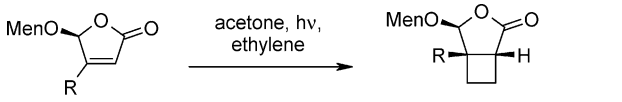


Figure 2. Model of the radical tandem reaction mechanism according to Hoffmann et al.[30b]

Scheme 26. [2+2]-Photoaddition of Ethylene According to Scharf et al.[33]



4b (R = H),
44b (R = Me),
57 (R = Cl)

58a (- 85°C, 75%, 47 % *d.e.*)
58b (- 25°C, 100%, 9 % *d.e.)*
58c (- 70°C, 100%, 20 % *d.e.)*

cycloadducts **61** was isolated in 80% yield based on a conversion of 45% (see Scheme 28).

A distinct facial selectivity was observed, namely, a ratio of adducts (**61a** + **61b** + **61d**):**61c** = 82:18, which reflects an *anti*-approach of the enone relative to the menthyloxy group. The formation of *endo*-product **61b** can be explained by the steric hindrance in the β-position of isophorone, as this is not observed if non-substituted cycloenones are employed.

The appearance of the more polar regioisomer **61d** could be accounted for by the use of acetonitrile as a comparatively polar solvent. Nonetheless, all isomers were separable by chromatography.

A new route to (+)-biotin **66** was pursued by researchers of Merck KGaA.[35] Commencing with a [2+2]-cycloaddition of chlorosulfonyl isocyanate to menthyloxy furanone **4a** (see Scheme 29), bicyclic lactam **62** is conceived stereoselectively. Subsequent conversion with sodium azide in water and successive heating followed by sulfite reduction gives the crystalline imidazolone **64** in 48% overall yield.

Cleavage of menthol proceeds smoothly under acidic conditions, followed by borohydride reduction to give the skeletal structure of (+)-biotin-precursor **65**. Advantages of this synthesis are the nonracemic assembly of the fused five rings and the low cost of the chiral chaperone, namely, (−)-menthol.

2.1.8. Cyclopropanation

The final example presented stems again from the inventors of menthyloxy furanone **4**, researchers of the former French company Roussel Uclaf, who cyclopropanated **4** enantioselectively with sulfur ylides (see Scheme 30).

Addition of isopropylidene diphenylsulfurane from the less shielded side under elaborate conditions gave the bicyclic system **67** with excellent selectivities. Treatment with aqueous perchloric acid results in ring opening of the lactone, and aldehyde **68** is received as a sound starting material for the insecticide deltamethrin (**69**).[36]

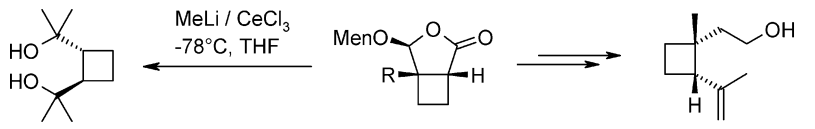
2.2. Dimenthyl Fumarate

2.2.1. Synthesis

Dimenthyl fumarate (**71**) is easily accessible via direct esterification of fumaric acid[37] or starting from fumaroyl chloride.[38] Yet, the most prevalent approach uses maleic anhydride (**70**) as the starting material (see Scheme 31).[39] Double esterification and subsequent isomerization of the double bond in the presence of morpholine yields **71** on a multigram scale.

This protocol has been applied to (−)-menthol[39b] as well as to its non-natural counterpart (+)-menthol[39c] on a larger

Scheme 27. Synthesis of (+)-Grandisol (60) and the Enantiopure Diol 59 by Scharf et al.[33]

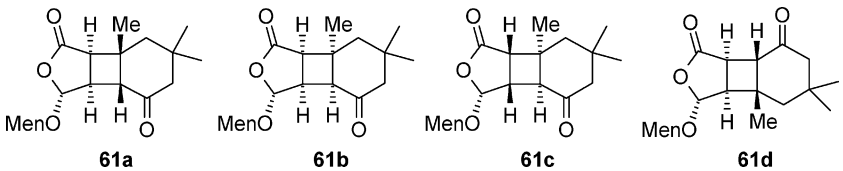


(*R*,*R*)-(+)-**59**

58b (R = Me),
58c (R = Cl)

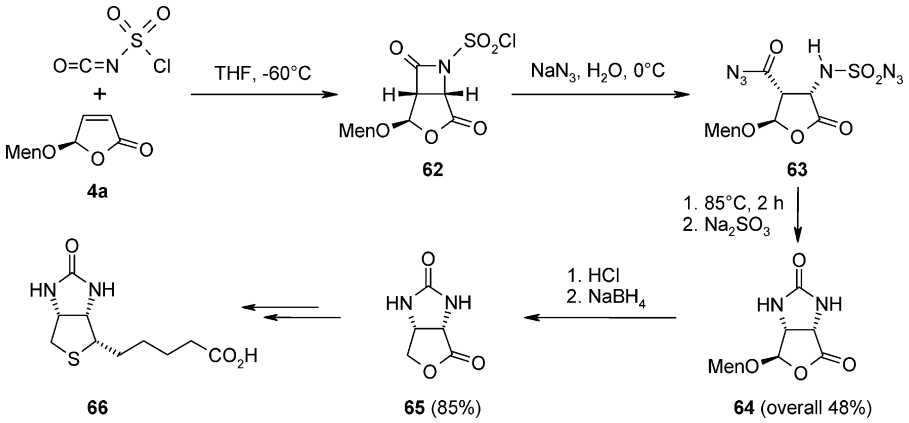
60, (+)-*grandisol*

Scheme 28. Photoaddition of Isophorone to Butenolide 4a According to Hoffmann et al.[34]

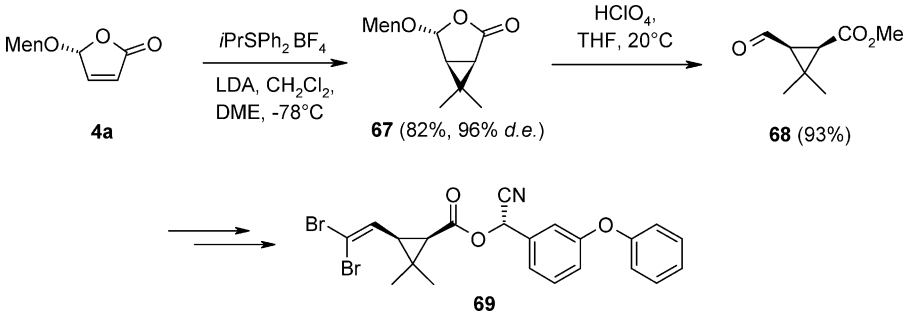


61a **61b** **61c** **61d**

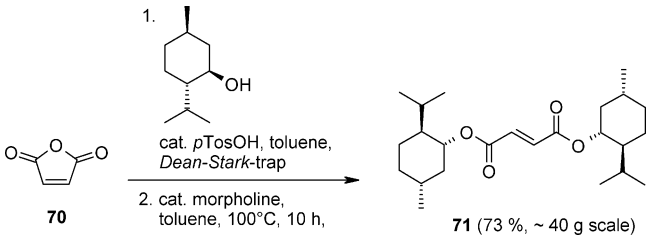
Scheme 29. Synthesis of Enantiopure (+)-Biotin (66)[35]



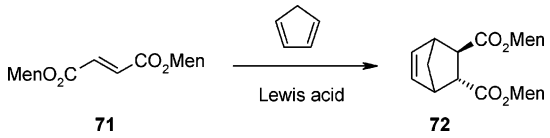
Scheme 30. Synthesis of Deltamethrin (69) According to Krief et al.[36]



Scheme 31. Synthesis of Dimenthyl Fumarate According to Yoshihara et al.[39]



Scheme 32. Diels−Alder Reaction of Dimenthyl Fumarate with Cyclopentadiene[40]



scale, as **71** was used as the starting material for natural product synthesis.

2.2.2. Diels–Alder Reactions

The Diels−Alder reaction of dimenthyl fumarate **71** as dienophile with various dienes is among the most carefully investigated reactions in "menthol-derived" chemistry. Initially, it was invented by Walborsky et al.[40a,b] and later optimized by Yamamoto et al.[40c] This reaction is exemplified for cyclopentadiene in Scheme 32.

The reaction has to be catalyzed, and some examples employing exclusively aluminum as the active Lewis-acidic metal are summarized in Table 2. However, catalysis of this reaction is clearly not restricted to aluminum Lewis acids: titanium and stannic chloride proved to be very effective as well.

Table 2. Asymmetric Diels−Alder Reaction of Dimenthyl Fumarate with Various Dienes[40]

diene	Lewis acid	equiv	temp (°C)	solvent	yield (%)	% de
butadiene	*i*-Bu_2AlCl	2.0	−40	hexane	56	95
isoprene	*i*-Bu_2AlCl	1.0	−20	hexane	94	95
cyclopentadiene	Et_2AlCl	1.0	−78	toluene	100	99
2,3-dimethyl-buta-1,3-diene	Et_2AlCl	1.0	−20	toluene	70	96
anthracene	$AlCl_3$	2.0	25	toluene	92	99

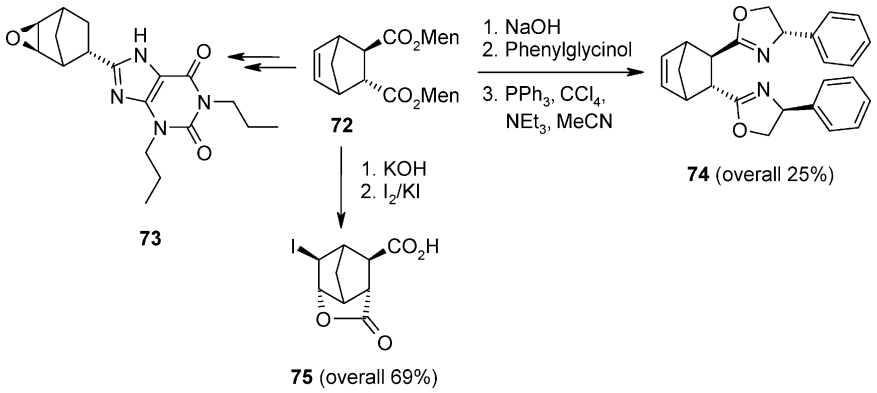
Generally, the cycloaddition proceeds with excellent diastereoselectivities but only in the presence of a Lewis acid catalyst. As with most stereoselective reactions, strong dependency of the diastereoselectivity on the temperature is observed; for example, at −78 °C almost complete selectivity is determined for the addition of cyclopentadiene, whereas at −20 °C the de drops to 91%.

Diels−Alder Reaction with Cyclopentadiene. Diels−Alder reaction with cyclopentadiene yields product **72**, which was used as a scaffold for a diverse set of applications (see Scheme 33): Takacs et al.[41] used the bicyclic system as a backbone for chiral bis(oxazoline) ligand **74**, which could be prepared via hydrolysis, amide formation with (*S*)-phenylglycinol, and final cyclization in an overall 25% yield starting from **72**. Both enantiomers of **72** are accessible, and in case of the (+)-menthol-derived dimenthyl fumarate cycloaddition affords the (2*R*,3*R*) absolute configuration of **72**.

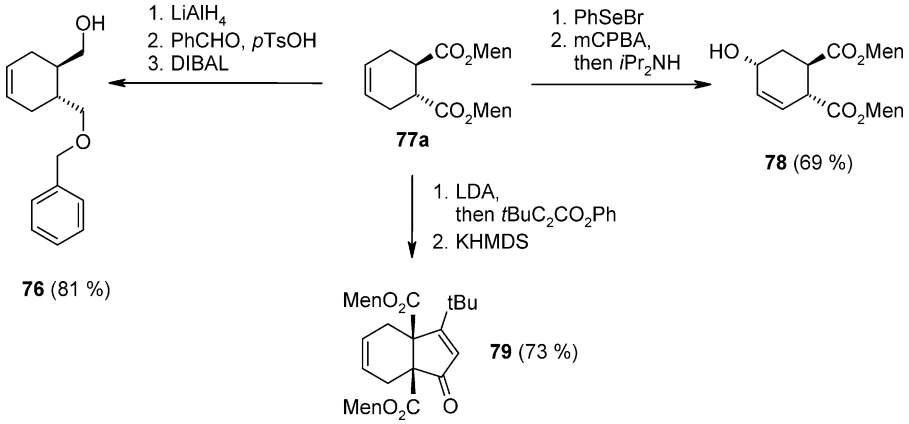
Hamanaka and co-workers[42] obtained the optically pure iodolactone **75** in 69% yield starting from di-(+)-menthyl fumarate. Straightforward saponification and iodolactonization gave intermediate **75**, which was further converted into a thromboxane A_2 antagonist.

Kiesman et al.[38d] reported on the synthesis of a different antagonist, namely adenosine A1 antagonist BG9719 (CVT-124) **73**: scale-up of pharmaceutical intermediate **72**

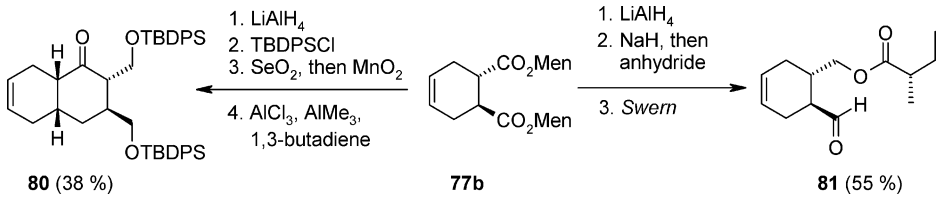
Scheme 33. Enantiomerically Pure Bicyclo[2.2.1]hept-5-ene-2,3-diester 72 as a Precursor



Scheme 34. Use of Enantiopure Cyclohexene 77a in Different Natural Product Syntheses



Scheme 35. Enantiopure Bis-ester 77b as Starting Material



is adressed with a focus on reaction temperature, toxicity of the Lewis acid, and recovery of menthol as chiral auxiliary.

Diels−Alder Reaction with 1,3-Butadiene. Diels−Alder reaction with 1,3-butadiene yields cyclohexene **77a**, a useful building block for different synthetic challenges (see Scheme 34). Recently, Ley et al.[43,39c] employed this *trans*-diester in their total synthesis of polycephalin C, a naturally occurring tetramic acid. Allylic alcohol **78** was generated from **77a** in 69% overall yield and formed the asymmetric central cyclohexene unit of polycephalin C.

The yield of the cycloaddition is reported to be 73%, accompanied by a selectivity of >95% de. Diethylaluminumchloride was the Lewis acid of choice and −60 °C the corresponding reaction temperature.

When the reaction was conducted in a mixture of hexane and dichloromethane at −40 °C, Solladié et al.[44] reported a yield of 98%, affording cyclohexene **77a** with a selectivity higher than 90%. Diester **77a** then was transformed into monoprotected diol **76** with an overall yield of 81%. Building block **76** is employed as an intermediate in their enantioselective synthesis of (+)-brefeldin A and already exhibits the desired stereochemistry, for it is transformed into the five-ring unit of the target molecule at a later stage of the synthesis.

Corey et al.[45] commenced their enantioselective synthesis of bilobalide, a C_{15} ginkgolide with a double addition sequence of *t*-butylacetylene phenylcarboxylate to bis-ester **77a**, resulting in the *cis*-bicyclic system **79** in 73% yield. It is noteworthy that all of the above examples started from (+)-dimenthyl fumarate obtained from "non-natural" (+)-menthol.

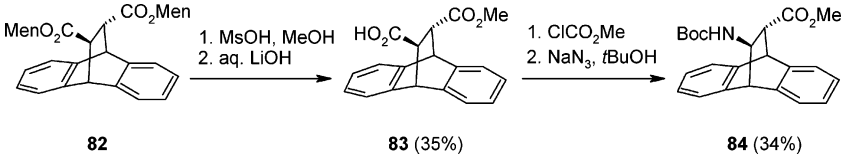
Using (−)-dimenthyl fumarate, Griesinger, Koert et al.[46] reported the synthesis of the (1*S*,2*S*)-enantiomer **77b**, which was converted into the bicyclic system **80**, resembling a precursor for a molecular *cis*-decalin switch (see Scheme 35).

This decalin-scaffold can be obtained from **77b** via an alanate reduction, successive protection of the diol, oxidation, and an aluminum-catalyzed Diels−Alder reaction with butadiene.

The same building block was converted into aldehyde **81** by Heathcock and co-workers in 1989 in an overall 55% yield.[39b] This sequence comprises a straightforward $LiAlH_4$ reduction, mono-esterification, and final oxidation. Compound **81** served as an intermediate in their synthesis of a monocyclic mevinolin analogue, used for the treatment of hypercholesterolemia.

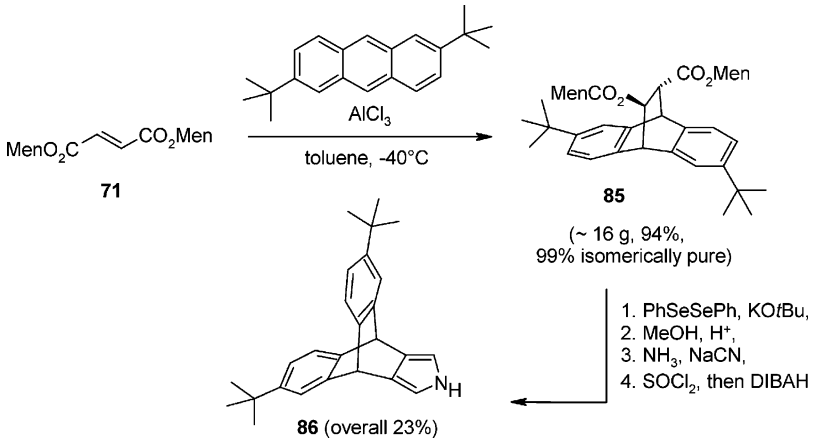
Diels−Alder Reaction with Anthracene. The asymmetric Diels−Alder reaction involving dimenthyl fumarate pro-

Scheme 36. Synthesis of Conformationally Rigid *β*-Amino Acid Derivative 84 According to Winkler, Axelsen et al.[48]



82 **83** (35%) **84** (34%)

Scheme 37. Synthesis of Enantiopure C_2-Symmetrical Pyrrole 86 According to Kräutler et al.[49a]



vides access to optically active C_2-symmetric dicarboxylic acid derivative **82**. Most commonly, $AlCl_3$ is chosen as the catalyst for the cycloaddition with anthracene, and standard transformations of **82** like ester hydrolysis or $LiAlH_4$ reduction to the corresponding diol have been described.[41,47]

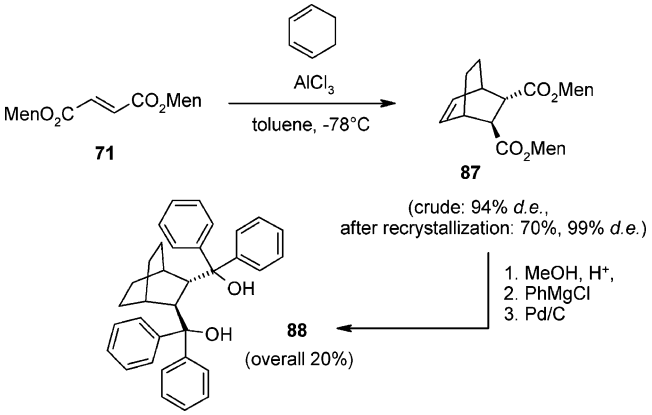
The conversion of chiral building block **82** to monoprotected *β*-amino acid **84** was accomplished via a transesterification reaction and successive monohydrolysis to give **83** in 35% yield (see Scheme 36). Curtius reaction of the acyl azide derived from **83** results in the *N*-Boc-protected amino ester **84**.[48]

Substituted anthracenes[49] have been employed by Kräutler et al.: cycloaddition of 2,6-di-*t*-butylanthracene[49a] to (−)-dimenthyl fumarate with $AlCl_3$ as Lewis acid catalyst gave gram quantities of **85** in excellent yields and selectivities (see Scheme 37).

Diester **85** was then oxidized to the corresponding maleic acid dimenthyl ester and after transesterification with methanol transformed into chiral pyrrole **86**, which served as a precursor for a biconcave porphyrin.

Diels−Alder Reaction with Cyclohexadiene. A further example applying this methodology is Seebach's conversion of cyclohexadiene via **87** to Taddol analogue **88** (see Scheme 38).[50]

Scheme 38. Seebach's Approach to Taddol Analogue 88[50]

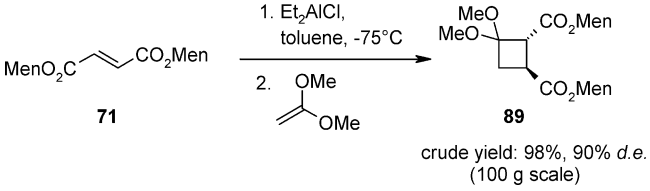


$AlCl_3$-catalyzed addition of cyclohexadiene to (−)-dimenthyl fumarate in toluene yields a crude product with 94% de selectivity, which is further enhanced by recrystallization from ethanol. The obtained (2*S*,3*S*)-bicyclo[2.2.2]octene derivative **87** is then transformed into the bis-methylester, which is submitted to an excess of phenyl Grignard reagent. Bidentate ligand **88** is received after hydrogenation and was examined for its enantioselectivity in the addition of organometallics to benzaldehyde.

2.2.3. [2+2]-Cycloaddition

Pericyclic reactions comprise [2+2]-cycloadditions, which are performed easily with dimenthyl fumarate (**71**) (see Scheme 39) and ketenacetals in the presence of dialkylaluminum chloride.[51]

Scheme 39. [2+2]-Cycloaddition Affording Chiral Cyclobutanones According to Ahmad[51a]

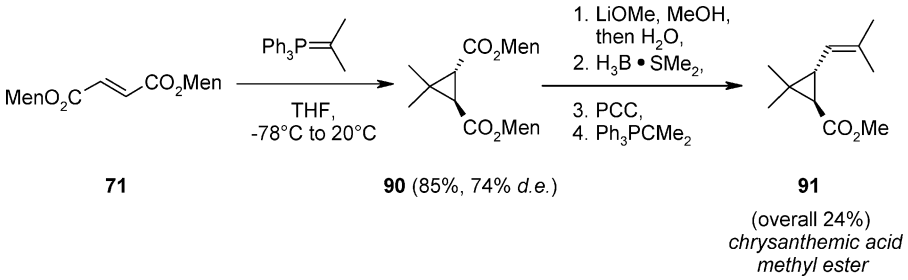


The addition proceeds smoothly at −75 °C and yields 83% diastereomerically pure **89** after recrystallization from aqueous methanol.[51a] This protocol was later modified by Brunner:[51b] the amount of Lewis acid catalyst can be reduced by replacing dialkylaluminum chloride with a corresponding quantity of inexpensive Hünig base. Doing so, it is even possible to perform this reaction at around −20 °C, resulting in 74% yield of diastereomerically pure material after recrystallization. Cyclobutanones **89** are of considerable interest as synthetic intermediates en route to antiviral nucleoside analogues.

2.2.4. Cyclopropanation

As early as 1983 Krief et al.[52] synthesized derivatives of chrysanthemic acid known for their insecticidal activity via

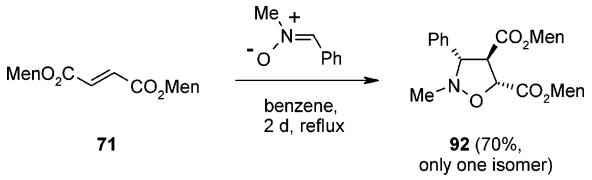
Scheme 40. Enantioselective Synthesis of Pyrethroid Derivatives According to Krief et al.[52]



71 **90** (85%, 74% *d.e.*) **91**

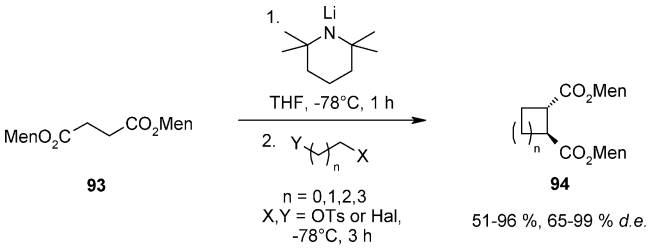
(overall 24%)
chrysanthemic acid methyl ester

Scheme 41. Formation of *all-trans* Isoxazolidine 92 via Nitrone 1,3-Dipolar Cycloaddition[53]

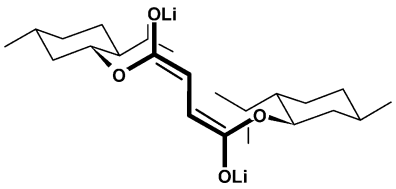


71 **92** (70%, only one isomer)

Scheme 42. Direct Coupling of Dimenthyl Succinate (93) with 1,ω-Dihalides[54]



93 **94** 51-96 %, 65-99 % *d.e.*



s-trans-(*E*,*E*)-Enolate from **93**

isopropylidene triphenyl phosphorane addition to dimenthyl fumarate (see Scheme 40).

Cyclopropane **90** was obtained in good yield and with satisfying selectivity. Further conversion implied recrystallization to furnish enantiopure **90** and subsequent transesterification under recovery of (+)-menthol. Final assembly of the isopropylidene unit is achieved via a selective monosaponification, conversion to the corresponding aldehyde, and concluding Wittig olefination to give pyrethroid **91** in 24% overall yield.

2.2.5. 1,3-Dipolar Cycloadditions

In the series of cycloadditions, a rare example of a 1,3-dipolar addition of nitrones to dimenthyl fumarate (**71**) was presented by Baskaran et al. (see Scheme 41).[53]

C-Phenyl-*N*-methyl nitrone adds smoothly to the (−)-menthol-derived bisfumarate to give only one isomer of the five-membered heterocycle **92**. The observed selectivity is rationalized by an *endo*-addition mode of the (*Z*)-nitrone.

2.3. Dimenthyl Succinate

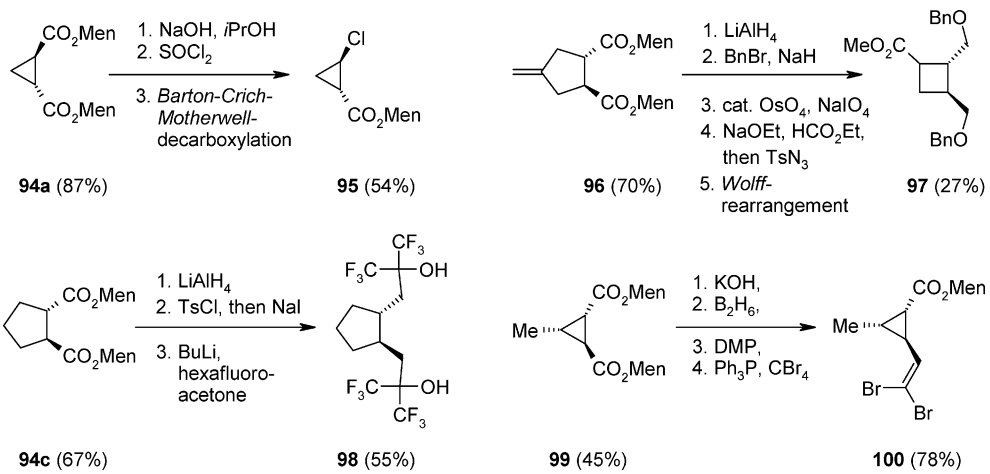
2.3.1. Synthesis

Dimenthyl succinate (**93**), the saturated analogue of dimenthyl fumarate (**71**), is a commercially available derivative of menthol. It is accessible via direct transesterification of succinic acid[54a] or succinic anhydride.[54b]

2.3.2. Yamamoto's Method

When **93** is treated with two equivalents of LiTMP in THF at −78 °C followed by subsequent addition of a 1,ω-dihalide, cyclic diesters **94** are formed. The diastereoselectivity is almost perfect (usually higher than 90% de), and yields range from good to excellent (see Scheme 42). An explanation for this remarkable stereoselectivity is given by Yamamoto and co-workers:[54a] the generated dilithium anion of **93** forms the *s-trans*-(*E*,*E*)-enolate selectively, which cyclizes readily with the corresponding dihalogen compound to the three-, four-, five-, or six-membered *trans*-esters. The procedure has expanded into the literature as Yamamoto's method.

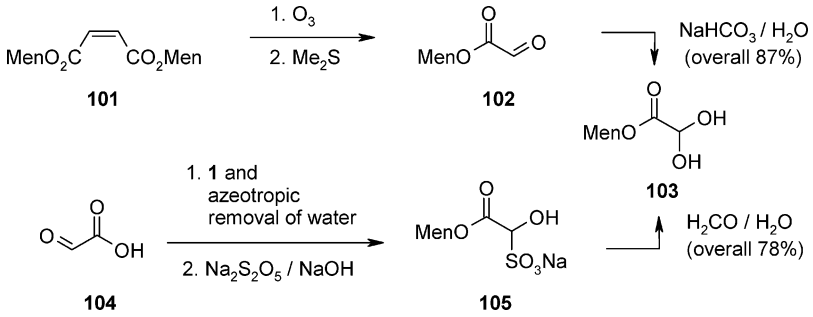
Scheme 43. Applications of Yamamoto's Protocol



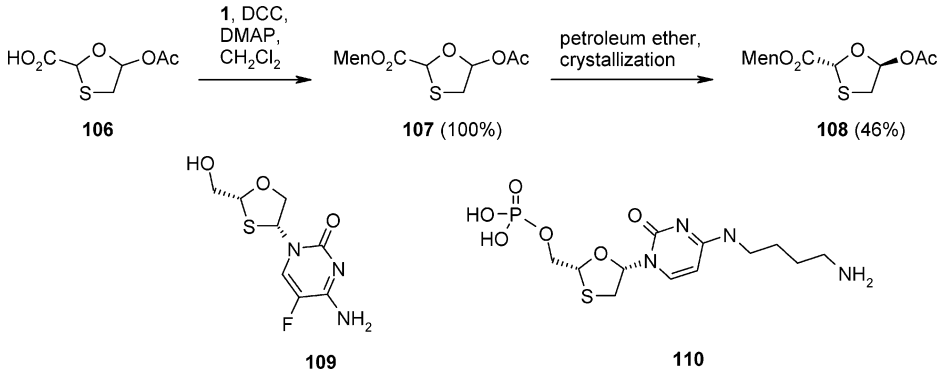
94a (87%) **95** (54%) **96** (70%) **97** (27%)

94c (67%) **98** (55%) **99** (45%) **100** (78%)

Scheme 44. Large-Scale Synthesis of Menthyl Glyoxylate Hydrate (103)[60,61]



Scheme 45. Synthesis of Chiral 1,3-Oxathiolanes



Because of its easy application and reliability in terms of selectivity, this method has found wide implementation in natural product synthesis. Recently, Trost and co-workers[55] prepared both enantiomers of cyclopropane **95** in the course of their total synthesis of callipeltoside A, a macrolide from a marine sponge (see Scheme 43). Isomerically pure building block **94a** was accessible in 87% yield according to Yamamoto's method and subsequently transformed into the mono acid chloride. Adjacent elimination of carbon monoxide gave cyclopropyl chloride **95** in good yield.

In 1996, Grubbs et al.[56] used this methodology for the synthesis of intermediate **94c**, a precursor of chiral ligand **98**, which was employed for the preparation of enantiopure molybdenum and tungsten metathesis catalysts. Again, both enantiomers of the ligand were prepared: commencing with dimenthyl succinate, five-membered ring **94c** was prepared in satisfying yields from 1,3-propanediol ditosylate on a 25 g scale. A straightforward reduction, iodination, and lithiation sequence followed by reaction with hexafluoroacetone gave ligand **98** in good overall yield.

Starting from (−)-dimenthyl succinate and 3-chloro-2-(chloromethyl)-1-propene, Kato et al.[57] synthesized isomerically pure compound **96** in 70% yield on a 30 g scale. It was then transformed into cyclobutane **97**, an interesting intermediate for carbocyclic analogues of nucleoside bases: the key steps of this ring contraction are the oxidation of the double bond followed by a Wolff-rearrangement of the corresponding diazoketone (see Scheme 43).

Kende et al.[58] utilized the dianion strategy in their total synthesis of ambruticin, an antifungal antibiotic, which exhibits a linking bis-vinylcyclopropane moiety in the central chain. Accordingly, cyclopropane **99** was obtained from 1,1-bromochloroethane and (−)-dimenthyl succinate in a moderate 45% yield after chromatography in enantiopure form. It was transformed into intermediate **100**, which establishes the desired stereochemistry of this middle fragment of (+)-ambruticin: selective monohydrolysis of **99**, followed by a reduction−oxidation sequence and concluding one-carbon homologation gave dibromomethylene compound **100** in excellent yield.

2.4. Menthyl Glyoxylate

2.4.1. Synthesis

Several different methods are practically viable and described in the literature,[59] although none of them has found application on an industrial scale. Instead, chemists at Lonza synthesized glyoxylate **102** in a straightforward fashion via ozonolysis of maleate derivative **101**[39] as illustrated in Scheme 44 (for the synthesis of **101**, see also Scheme 31).[60]

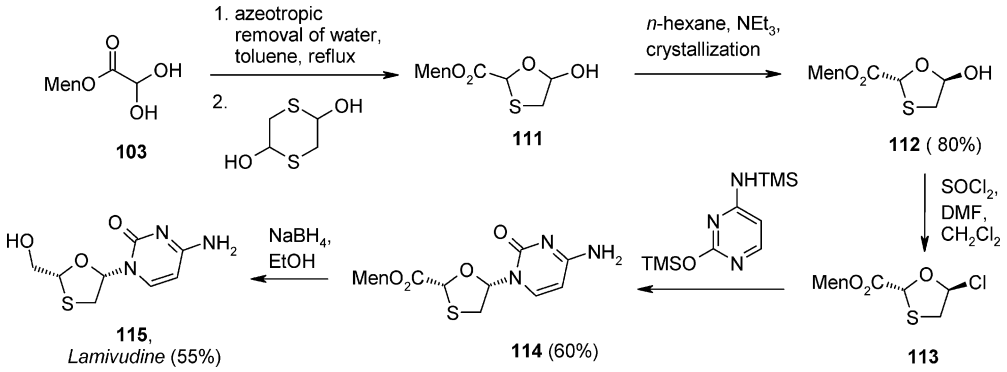
Glyoxylate **102** is isolated as the monohydrate **103** in a one-pot procedure with an overall yield of 87%. A different route (see Scheme 44) was applied by Hoechst chemists in 1995:[61] starting from glyoxylic acid **104**, monohydrate **103** was received in 78% yield after treating **105** with aqueous formaldehyde and without isolation of the intermediate sulfonic acid salt.

2.4.2. Synthesis of Chiral 1,3-Oxathiolanes

One recent application of menthyl glyoxylate (**102**) is the synthesis of 3TC or Lamivudine (**115**)[62] and its derivatives (see Schemes 45 and 46). Those compounds are nucleoside analogues characterized by a 1,3-oxathiolane ring used for the treatment of AIDS and hepatitis. Initially, menthol was simply utilized as a chiral resolving agent for building block **106** (see Scheme 45).

Acid **106** was converted into menthyl ester **107**, and crystallization from petroleum ether gave enantiopure precursor **108** in 46% yield (based on one enantiomer).[62b] This material was employed for the synthesis of a whole set of analogues, two of which are depicted in Scheme 45: **109** bearing its fluoro cytosine moiety in the uncommon

Scheme 46. Synthesis of Anti-HIV Agent Lamivudine (115)[62c]



4-position[63a] and **110** displaying the "traditional" substitution pattern but containing a monophosphorylated alcohol.[63b]

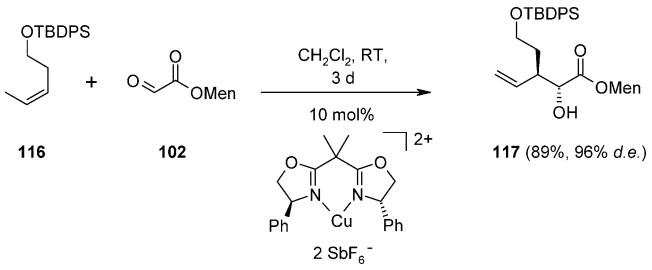
Recently, a very elegant approach for the synthesis of similar oxathiolanes has been published by Whitehead et al.,[62c] benefiting from menthol glyoxylate (see Scheme 46): construction of the oxathiolane **111** proceeds in a straightforward fashion, and successive dynamic kinetic resolution of **111** gives enantiopure **112** in an impressive 80% overall yield. Interconversion of the unwanted diastereoisomers is achieved by adding triethylamine, which epimerizes **111** at C-2. The desired product is removed from the equilibrium via crystallization.

Completion of the synthesis involves introduction of chlorine as the leaving group, coupling with the persilylated cytosine resulting in **114**, and reductive cleavage of the menthol auxiliary to give lamivudine (**115**) in an overall practical 55% yield.

2.4.3. Ene Reaction

Although menthyl glyoxylate (**102**) was employed in Lewis acid catalyzed ene reactions since the 70's,[64a] its application as a chiral auxiliary for this purpose has been outranked by the utilization of the corresponding 8-phenylmenthol derivative,[3] mostly because selectivities for the latter are superior.[64b,c] Nevertheless, the advantages of low cost and easy large-scale preparation legitimate the use of **102** (see Scheme 47).[64d]

Scheme 47. Double Asymmetric Ene Reaction According to Rozners et al.[64d]



Consequently, in their synthesis of azido nucleoside acids, Rozners et al. applied a copper-bisoxazoline as a Lewis acid catalyst to enhance selectivities of the pericyclic reaction. Homoallylic alcohol **117** was obtained in good yield and excellent selectivity, when a tenfold excess of glyoxylate **102** was employed.

2.4.4. Hetero-Diels–Alder Reaction

Pyrone-type compound **119** was envisioned by Mulzer et al.[65a] in 1995 as an intermediate for a total synthesis of swinholide A. The Lewis acid catalyzed hetero-Diels−Alder reaction of diene **118** with **102** and subsequent desilylation afforded almost exclusively *trans*-**119** as a 1:1 diastereomeric mixture. Switching to 8-phenylmenthol as an auxiliary improved selectivity and gave **119** in diastereomerically pure form.

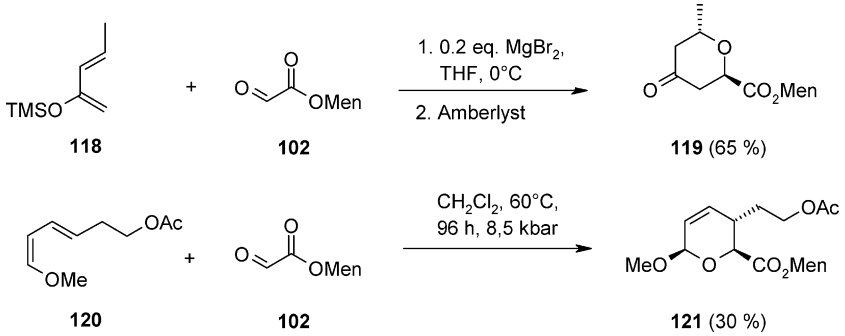
Aiming at the dihydropyran system **121**, Schmidt et al.[65b] submitted *cis*-*trans*-hexadiene derivative **120** (see Scheme 48) to a thermal hetero-Diels−Alder reaction resulting in a mixture of three isomers. Isomer **121**, displaying the required stereochemistry for further interconversion to thromboxane derivatives, was isolated in a yield of 30%.

2.4.5. Friedel–Crafts Reaction

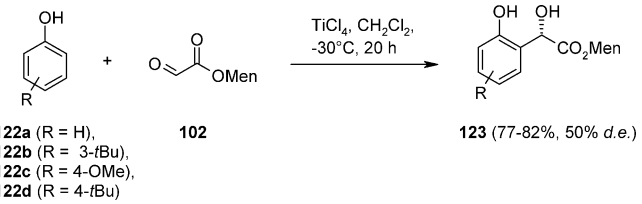
In 1990, Bigi et al.[66] presented an asymmetric Friedel−Crafts reaction involving a phenol **122** and menthyl glyoxylate (**102**) in the presence of titanium tetrachloride, which was the Lewis acid of choice. Conversion at low temperatures gave good yields for several phenols but modest selectivities in all cases (see Scheme 49).

By switching to menthyl pyruvate (**124**),[67a] different procedures have been reported:[67] by staying with titanium

Scheme 48. Pyran-type Building Blocks via Hetero Diels−Alder Reaction



Scheme 49. Synthesis of 2-Hydroxy Mandelic Esters According to Bigi et al.[66]



122a (R = H), **122b** (R = 3-*t*Bu), **122c** (R = 4-OMe), **122d** (R = 4-*t*Bu) **102** **123** (77-82%, 50% *d.e.*)

tetrachloride, but additionally applying one equivalent of menthol as chiral co-ligand, selectivities could be drastically improved (see Scheme 50); reaction with phenol derivatives **122b** and **128** results in selectivities of up to 82% de.[67b,e] Amazingly, 1-naphthol (**126**) does not require the addition of menthol.

At −60 °C and in the presence of sodium carbonate, **127** is obtained in excellent yield and diastereomeric excess.[67c,d] This concept was successfully applied in natural product synthesis: Hauser et al.[67e] prepared optically active atrolactic acid derivative **129** on a 15 g scale and used it as a precursor for the aminoepoxybenzoxocin entity in antitumor agent nogalamycin.

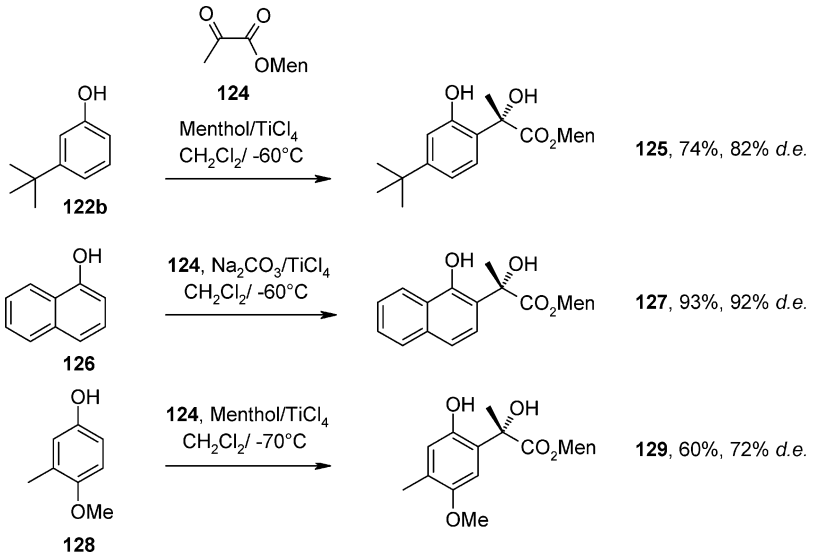
2.4.6. Addition of Organometallic Compounds

Several examples are described in the literature,[68] and usually Grignard reagents or organozinc compounds add to the α-carbonyl moiety of an α-keto menthyl ester.

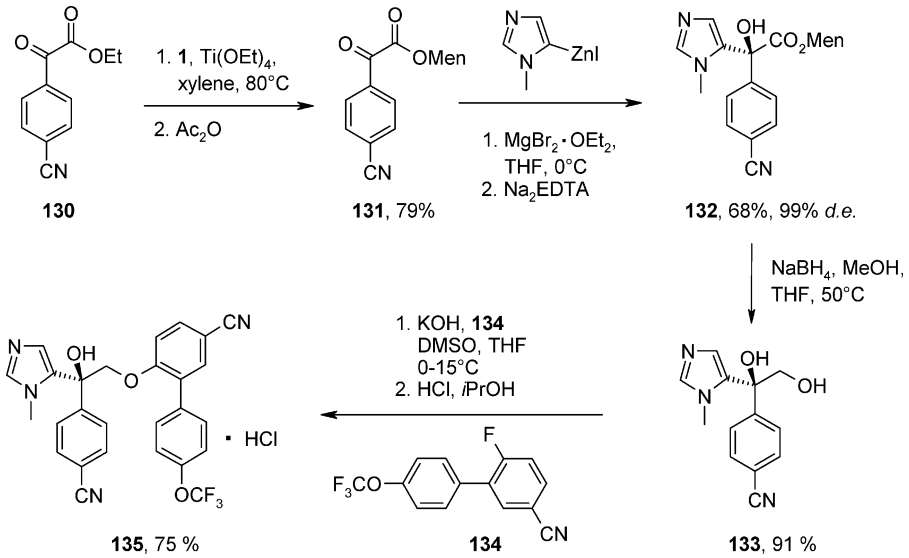
This methodology was applied in the total synthesis of ABT-100 (**135**), a farnesyl transferase inhibitor, which was investigated by researchers at Abbott (see Scheme 51).[69] The synthesis is performed on a kilogram-scale, and the choice for menthol is elucidated by the authors: "*Use of menthol as the chiral auxiliary provides many advantages: low cost, availability, good selectivity and a tendency for intermediates to be crystalline.*"

Starting from commercially available phenylglyoxylic ester derivative **130**, which is transesterified with (−)-menthol

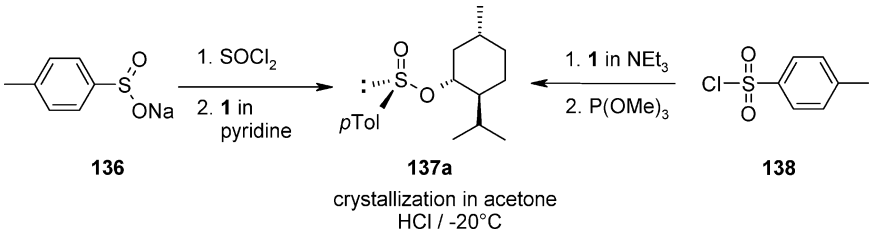
Scheme 50. Addition of Menthyl Pyruvate (124) to Aromatic Systems



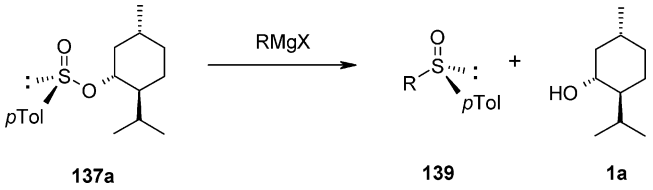
Scheme 51. Synthesis of 1 kg of Enantiopure ABT-100 (135) According to Rozema et al.[69]



Scheme 52. Large-Scale Synthesis of Enantiopure Sulfinate 137a According to Solladié et al.[72] and Sharpless et al.[73]



Scheme 53. Andersen's Method for the Synthesis of Optically Pure Sulfoxides 139[74]



according to a protocol developed by Krasik,[70] optically active α-keto ester **131** is obtained in 79% yield. Subsequently, unreacted menthol is quenched in situ with acetic anhydride and after work-up the resulting mixture is submitted to a Lewis acid promoted addition. Imidazolyl zinc iodide adds to **131** in the presence of $MgBr_2$ and affords tertiary alcohol **132** with a diastereomeric ratio of 11:1. Employing the analogous Grignard reagent gave much lower selectivity, and without the presence of Lewis acid $MgBr_2$ no reaction takes place. The product is isolated as a crystalline dimeric zinc complex; liberation of the alcohol **132** is achieved by treatment of the complex with disodium EDTA. Following this procedure, the diastereomeric ratio of **132** was increased to greater than 99:1. Reduction, successive S_NAr-reaction with electron-deficient fluoro biphenyl **134** and final precipitation as hydrochloride affords the target molecule **135** in an enantiopure form in 37% overall yield.

2.5. Menthyl *p*-Toluenesulfinate

2.5.1. Synthesis

Menthyl *p*-toluenesulfinate (**137**) was first examined within the context of chirality and optical rotation by Phillips in 1925,[71] but it became most popular due to the preparation of optically active sulfoxides in the 1960s. This chiral building block is most commonly synthesized by two different procedures. Solladié et al.[72] established a procedure starting from the sodium salt of *p*-toluenesulfinic acid **136** (see Scheme 52). In a convenient fashion, the diastereomeric products are equilibrated by addition of hydrochloric acid, and (*S*)-(−)-menthyl *p*-toluenesulfinate (**137a**) is obtained in pure form with 65% yield.

This well-described procedure affords up to 60 g of the desired sulfinate **137a**.

In 1987, Sharpless et al.[73] published an alternative method, using sulfonyl chloride **138** as starting material (see Scheme 52) and trimethylphosphite as the in situ reducing agent. Epimerization at the sulfur center takes place in the same fashion, as well as the crystallization of the (*S*)-enantiomer in acetone.

2.5.2. Synthesis of Enantiopure Sulfoxides: Andersen's Method

The property of **137** that is most frequently taken advantage of is the addition of organometallics with the simultaneous loss of the menthol moiety. Nucleophilic attack at the sulfur center results in complete inversion of the configuration. "*In other words, optically pure sulfinate esters yield optically pure sulfoxides*", which was first described by Andersen[74] using Grignard reagents (see Scheme 53).

This procedure has found widespread application in the synthesis of *p*-tolyl alkyl or aryl sulfoxides. Because of its frequent use, compound **137** has therefore been coined "Andersen's reagent". Switching to different organometallic nucleophiles, which can even be highly functionalized, has opened the field to a whole class of chiral sulfoxides derived from menthol. For an in-depth study of their applications, refer to the literature.[75]

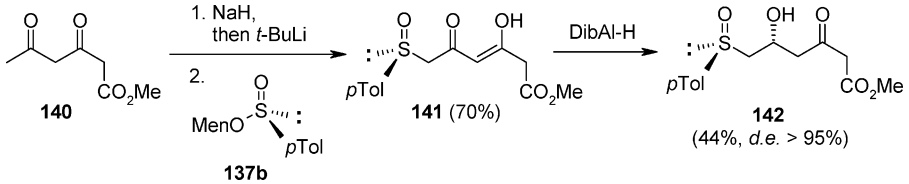
2.5.3. Solladié's Diketosulfoxide

Some recent examples are presented in Scheme 54: Solladié et al.[76] converted the trianion of dioxo ester **140** with menthyl toluene sulfinate **137b** into enantiopure diketosulfoxide **141**. Adjacent reduction takes place regio- and stereoselectively, but the product **142** has to be separated from starting material and a *p*-ditolyl disulfide byproduct. Crystallization from ether/dichloromethane afforded pure **142** in yields ranging from 42 to 66% (see Scheme 54).

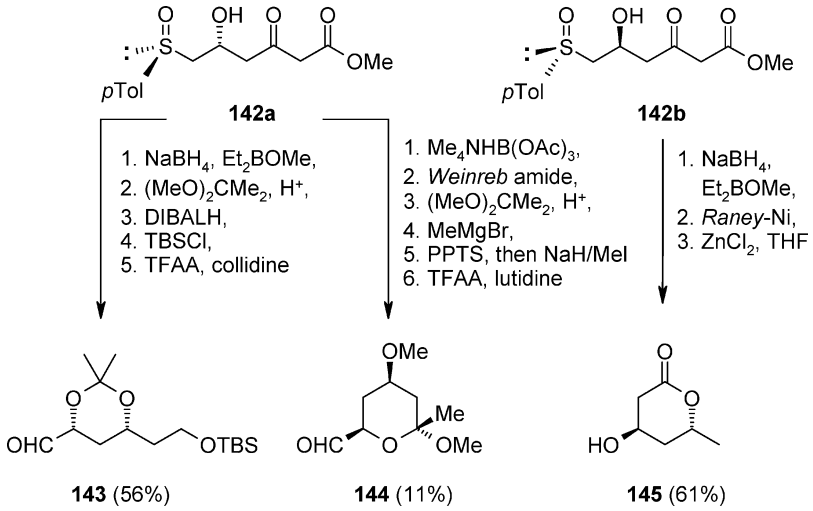
With compound **142** in hand, a variety of structurally very diverse intermediates have been successfully prepared (see Scheme 55): aldehyde **143** was employed in the synthesis of the polyol fragment of amphotericin B. It is accessible from **142a** via a reduction of the keto group, acetonide formation, reduction of the ester moiety, and final liberation of the aldehyde through a Pummerer reaction in an excellent 56% overall yield.[76a]

Tetrahydropyran ring **144** occurs naturally as a fragment of phorboxazoles A and B; both marine sponge macrolides display inhibition of tumor cell growth. Again, keto group reduction of **142a** to the corresponding diol, transformation of the ester moiety into a methyl ketone, and intramolecular hemiketalization affords the THP-scaffold. The concluding

Scheme 54. Synthesis of Key Intermediate Hydroxysulfoxide 142[76]



Scheme 55. Intermediate 142 in Different Natural Product Syntheses[76]



Pummerer reaction gives aldehyde **144** as the only diastereomer in optically pure form and 11% overall yield.[76c]

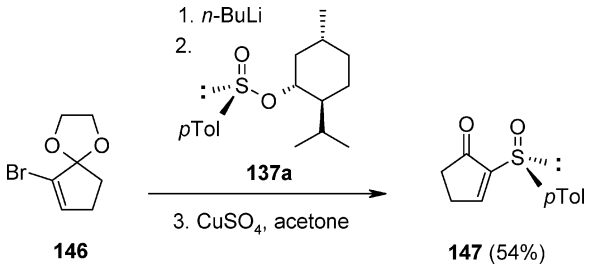
The synthesis of both aldehydes **143** and **144** benefits from the commercial availability of "unnatural" (+)-menthol, used as the starting material for menthyl toluenesulfinate **137b**.

Lactone **145** is one key intermediate in Solladié's total synthesis of (−)-colletol, an unsymmetrical bismacrolide first isolated in 1973. Employing the same synthetic strategy, but this time starting from natural (−)-menthol, desulfurization of reduced **142b** with Raney-nickel and zinc-mediated lactonization of the corresponding hydroxy ester results in the formation of lactone **145** in 61% yield.[76b]

2.5.4. p-Toluenesulfinyl-2-cyclopentenone

Directly derived from the menthyl sulfoxide **137a**, crystalline vinyl sulfoxide **147** is accessible in multigram quantities via lithiation of bromo ketal **146**, subsequent nucleophilic substitution of menthol at the sulfur center, and concluding deketalization in 54% overall yield (see Scheme 56).[77]

Scheme 56. Synthesis of Sulfinyl Cycloalkenone 147 According to Posner et al.[72d]



This building block was employed in the synthesis of 9,11-*seco* steroid **149** by Posner et al.[78] in 1982. Addition of a naphthyl Grignard reagent in a 1,4-fashion and subsequent quenching with methyliodide proceeded with 98% stereoselectivity (see Scheme 57).

Adjacent desulfurization of **148** with dimethylcopperlithium and alkylation with methyl bromoacetate gave the desired steroidal scaffold in the natural configuration.

2.5.5. p-Toluenesulfinyl-2-furan

This approach is not restricted to cyclopentenones but also applies for furans: when submitted to Andersen's procedure, furan is transformed into a chiral heteroaryl sulfoxide **150** (see Scheme 58).[79]

In contrast to the lithiated cyclopentene **146**, quantitative inversion is only achieved when the lithiated furan is transmetalated to magnesium using freshly prepared magnesium bromide. Various substituted furans and thiophenes have been prepared according to this method in enantiopure form, and yields usually exceed 75%.[79]

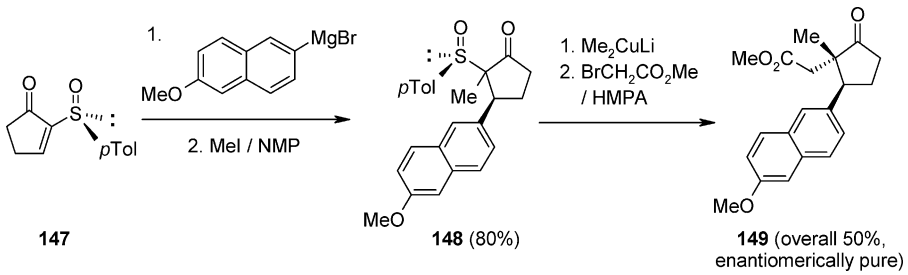
Montana et al.[80] investigated [4+3]-cycloaddition reactions of thirteen different chiral furans with oxyallyl cations (see Scheme 59). Among those furans, compound **150** was the most efficient in terms of selectivity.

Employing symmetric dihaloketone **151** as oxyallyl cation precursor allows formation of four possible diastereoisomeric cycloadducts out of which **152** is the one preferentially formed.

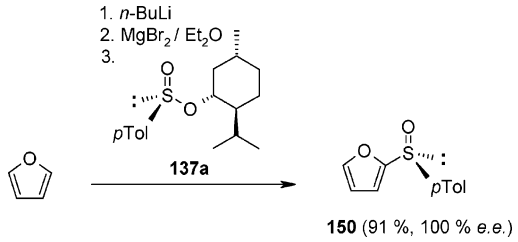
2.5.6. p-Toluenesulfinylquinone

Several chiral sulfinylquinones were prepared in 1992 by Carreño et al.[81] as depicted in Scheme 60. Starting from 1,4-dimethoxybenzene, a direct lithiation approach proved

Scheme 57. Posner's Formal Total Synthesis of Equilenin Derivative 149[78]

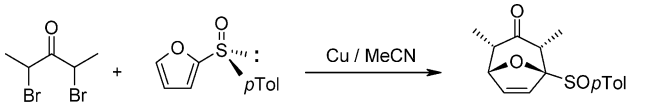


Scheme 58. Rouessac's Synthesis of Chiral Furan Derivatives[79]



150 (91 %, 100 % *e.e.*)

Scheme 59. Synthesis of Cycloheptene Moiety According to Montana et al.[80]



151 **150** **152** (51 %, 46 % *d.e.*)

to be superior to a bromination/lithium-bromine exchange sequence. Remarkably, for obtaining good ee values, no switch to the organomagnesium species was necessary. Subsequent oxidation of **153** with CAN gave the desired chiral quinone **154** in an overall yield of 68% in almost optically pure form.

One impressive example in which central chirality is effectively transformed into helical chirality was presented by the same group (see Scheme 61).[82] Chiral quinone **154** was submitted to a twofold Diels−Alder reaction with hydrocarbon **155** furnishing a helical heptacyclic system.

The initially formed cycloaddition/sulfoxide elimination product was further aromatized with DDQ, yielding the helicene **156** in overall 45% yield and excellent enantiomeric purity. The whole process can even be shortened to a one-pot procedure and is the first non-photochemical asymmetric approach toward helicene-bisquinones.

2.5.7. Synthesis of L-765,527

Another successful example for Andersen's strategy is outlined in Scheme 62. Researchers at Merck were facing the challenge of synthesizing relevant quantities of clinical candidate **162**, used for the treatment of asthma.[83]

Beginning with lithiated picoline, Andersen's methodology afforded chiral sulfoxide **157** in very good yield and multigram quantities. Subsequent aldol addition to cyclopentyl isovanillin (**158**) is performed in the presence of sodium amylate, resulting in the formation of one single diastereomer of the addition product **159**. Straightforward elimination of the alcohol moiety gave **160** as the only isomer. 1,4-Addition of organometallic reagents to chiral vinyl sulfoxide **160** required vast optimization: yet excellent selectivities and yields could be achieved by the use of catalytic amounts of $Ni(acac)_2$ and preformed organozinc reagents. Careful control of the reaction temperature and order of addition allowed for both selectivity and reactivity to exceed 90%. Simple desulfurization with zinc metal completes the synthesis in an overall yield of 38% and excellent enantiomeric excess.

2.5.8. Ferrocenyl p-Tolyl Sulfoxide

The chiral ferrocenyl *p*-tolyl sulfoxide (**163**) was, to the best of our knowledge, initially invented by Kagan et al.[84] in 1990.

It was shown that Andersen's method could be applied to ferrocene (see Scheme 63). Various procedures have been presented for its synthesis, mostly addressing the issues of generating pure monolithioferrocene optimizing yield and selectivity.[85]

The procedure depicted in Scheme 63 was described by Bäckvall et al. in 2003 as a result of careful optimization and appears to be the most convenient method so far.

Ferrocene is directly lithiated in the presence of potassium *t*-butoxide with *t*-butyllithium, and subsequent addition to **137a** in THF solution at −55 °C affords almost enantiopure ferrocenyl sulfoxide **163** in 80% yield.

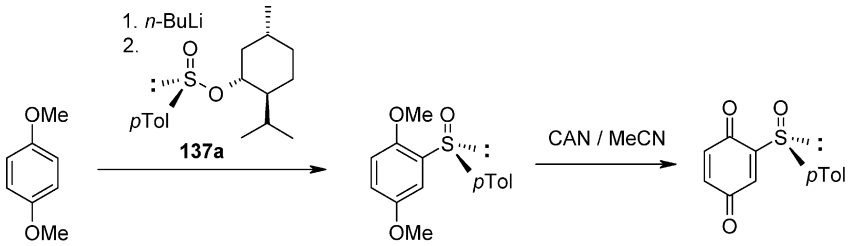
One outstanding property of this chiral sulfoxide is the fact that, if **163** is lithiated, the sulfoxide group exhibits a highly diastereoselective *ortho*-directing effect making planar chiral 1,2-substituted ferrocene-derivatives accessible (see Scheme 64). This was originally recognized by Kagan and co-workers[86] and further pursued to improve access to planar chiral ferrocenes.[85b]

The synthesis of planar-chiral phosphine ligands has especially attracted considerable interest, as those ligands are ubiquitous in enantioselective, transition-metal-catalyzed transformations. *Ortho*-lithiation of **163** with LDA and a subsequent transmetalation−Negishi cross-coupling sequence introduced the aryl moiety of **164** in a diastereo- as well as atroposelective fashion and excellent yield.

An even more intriguing feature of this sulfoxide approach becomes apparent in the next step: desulfurization is easily realized by lithiation, if **164** is treated with *t*-butyllithium. Direct trapping of the anion with chlorodiphenylphoshine affords the chiral monophosphine ligand **165** in enantiopure form. Its usefulness is demonstrated in the palladium-catalyzed asymmetric hydrosilylation of styrene, in which **165** exhibits an enantioselectivity of 90% ee and a remarkably high turnover frequency.[87a]

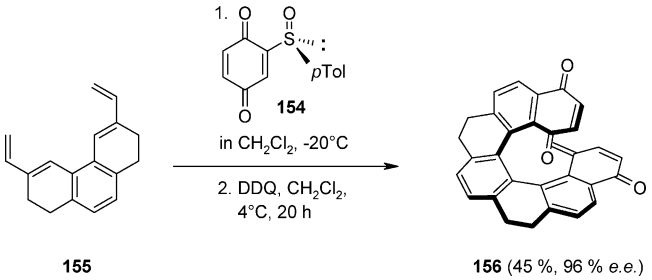
A different ligand design is achieved if the diphenylphosphine moiety is introduced in the first step, as has been demonstrated by Kagan and co-workers.[87b] Successive in situ protection of the phosphine with borane to avoid oxidation gives **166** in enantiomerically pure form. Sulfur substitution with chlorodimethylphosphine and deprotection result in

Scheme 60. Synthesis of Enantiopure *p*-Tolylsulfinylquinone According to Carreño et al.[81]



153 (75 %) **154** (90 %, *e.e.* > 95 %)

Scheme 61. Asymmetric Synthesis of Tetrahydro[7]helicene Bisquinone (*M*)-156[82]



planar chiral diphosphine ligand **167**. When **167** was employed in asymmetric rhodium-mediated hydrogenation, enantioselectivities of up to 95% ee were achieved.

2.5.9. Sulfinimines

Chiral sulfinimines **169** were originally prepared by addition of metalloimines (generated in situ by addition of Grignard reagents to nitriles) to Andersen's reagent **137a**.[88] Because of the low yields of this approach, Davis et al. developed the protocol depicted in Scheme 65, which was constantly improved over the years.[89]

The optimized procedure[89d] is a two-step process starting with the synthesis of enantiopure *p*-toluenesulfinamide **168**, which is converted into the desired sulfinimines **169** in the presence of titanium ethoxide. This protocol works for aldehydes as well as ketones, and in the case of aliphatic examples enolization does not occur due to the strong activation that the *N*-sulfinylgroup exerts on the C−N bond.

Sulfinimines **169** can be regarded as chiral ammonia imine synthons, providing a solution to the problems usually encountered when adding organometallics to imines: activation, powerful stereodirecting effects, and convenient cleavage of the S−N bond make them ideal building blocks in asymmetric synthesis.[90]

Researchers at Bristol-Myers Squibb examined different routes to produce the human leukocyte elastase inhibitor DMP 777 (**174**).[91] Key intermediate **173** was accessible via the original metalloimine protocol: addition of *n*-propyl magnesiumchloride to piperonylonitrile **170** and subsequent reaction with **137b** gave chiral sulfinimine **171**. Successive diastereoselective reduction with DIBALH followed by deprotection under mild acidic conditions gave the desired amine **173** with good selectivities (see Scheme 66).

Although it was not pursued further, this was the only route allowing for recovery of the chiral auxiliary. Moreover, it is noteworthy that in this case the applied Andersen's reagent **137b** was derived from "non-natural" (+)-menthol (**1b**).

Instead of reducing the chiral imine, DeGoey and coworkers benefited from the diastereoselective addition of silyloxypyrrole **176** to **175** (see Scheme 67). This represents the key step in their enantioselective synthesis of neuraminidase inhibitor **178** developed at Abbott laboratories.[92]

At −23 °C, the trimethylsilyl triflate mediated reaction proceeds smoothly to yield the crystalline diasteromer **177** exclusively, which was confirmed via single-crystal X-ray analysis. Employing the diastereomeric (*S*)-*p*-toluenesulfinimine leads to a reversal of the facial selectivity of the addition to the imine, demonstrating the dominating influence of the chiral sulfinyl group.

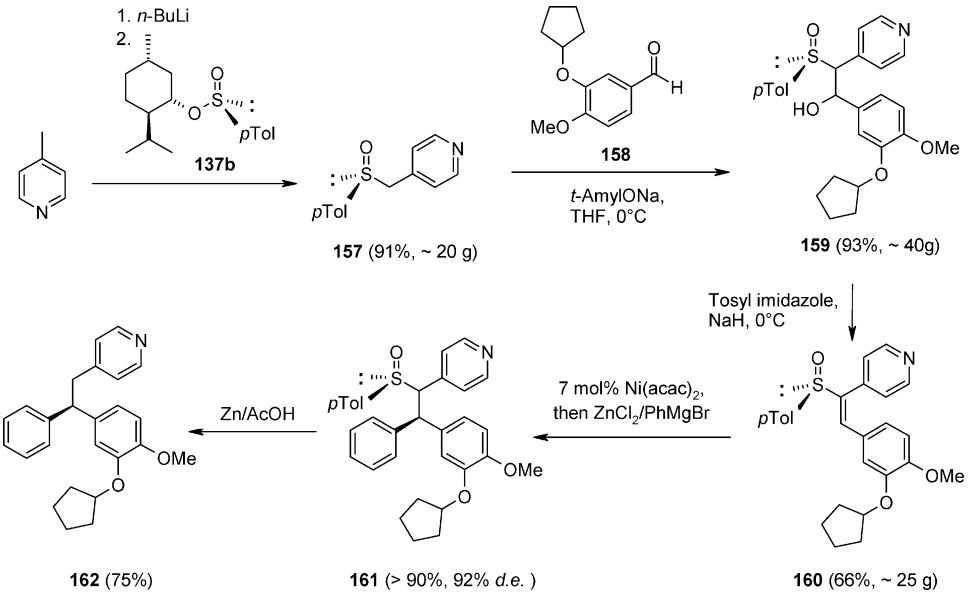
A further example demonstrating the synthetic utility of chiral sulfinimines was recently presented by researchers of Schering-Plough (see Scheme 68).[93] Access to optically active β-amino sulfones **181**, a biologically interesting structural motif, is achieved via addition of α-lithiated sulfones **179** (R = *t*Bu or adamantyl; R′ = Me) to imine **180**. This approach can be extended to β-amino sulfonamides [R = NMe_2, R′ = Me or R−R′ = $-NMe(CH_2)_2-$] and furnishes the desired products with very good yields.

The addition occurs with excellent stereocontrol and both the α- and β-stereocenters are formed with almost complete diastereoselectivity.

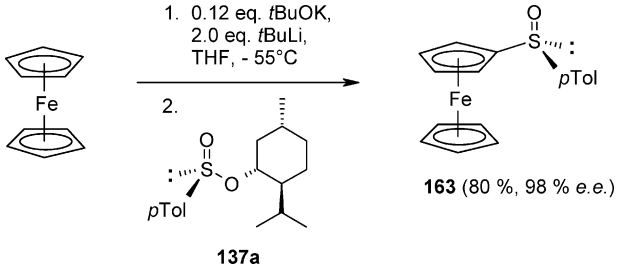
2.5.10. Sulfinamides

Optically pure sulfinamides **182** have continuously been prepared according to a straightforward addition of lithiated amines to Andersen's reagent.[94] Employing this approach, yields are commonly satisfactory and the products are formed via inversion at the sulfur center with exclusive selectivity but in one case (see Scheme 69): phenyl-*p*-toluenesulfinamide (**182b**) had to be recrystallized several times to obtain enantiomerically pure material.[94a]

Scheme 62. Total Synthesis of L-765,527 (162), a Phosphodiesterase IV Inhibitor[83]



Scheme 63. Synthesis of Ferrocenyl *p*-Tolyl Sulfoxide (163) According to Bäckvall et al.[85e]



To obtain high ee's careful control of the addition order is necessary; thus, the lithiated species has to be added to a solution of **137a**.

This strategy was used by Koomen et al.[94d] in their synthesis of enantiopure tetrahydro-β-carbolines **183** (see Scheme 70), a common motif in biologically active molecules. Chiral tryptamine derivative **182d** is cyclized with an aliphatic aldehyde in the presence of camphorsulfonic acid to afford the tricyclic system **183** as crystalline material.

Sometimes removal of auxiliaries is only realized under harsh conditions, causing racemization in the case of optically active materials. However, in this sequence applied here, the amine **183** could be liberated in high yields and without loss of optical activity under exceptionally mild conditions: complete removal was accomplished under acidic treatment within 5 min at 0 °C, and even recovery of Andersen's reagent was possible if cleavage was performed in the presence of (−)-menthol instead of ethanol.

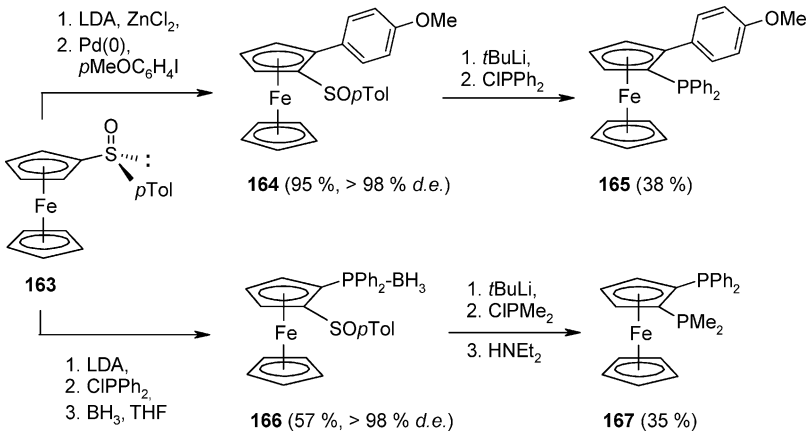
2.5.11. Derivatives of Andersen's Reagent

One derivative of the reliable Andersen's reagent that has received increased attention recently is the *p*-bromobenzenesulfinate **185** (see Scheme 71). Prepared from **184** according to the Sharpless protocol,[73a] two large-scale syntheses have been reported.[95]

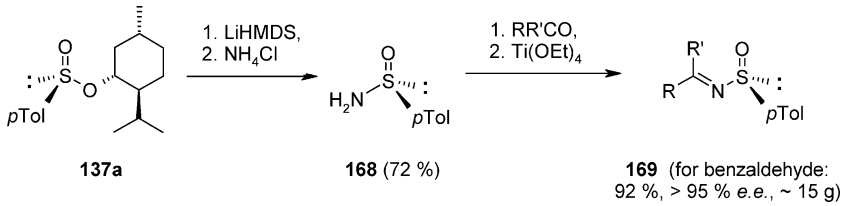
The optically pure material **185** is obtained by HCl-driven isomerization and repeated crystallization from acetone analogously to the synthesis of the *p*-tolylderivative **137** (see Scheme 52).

One intriguing aspect of this halo-Andersen reagent **185** is the possibility to perform a double replacement sequence

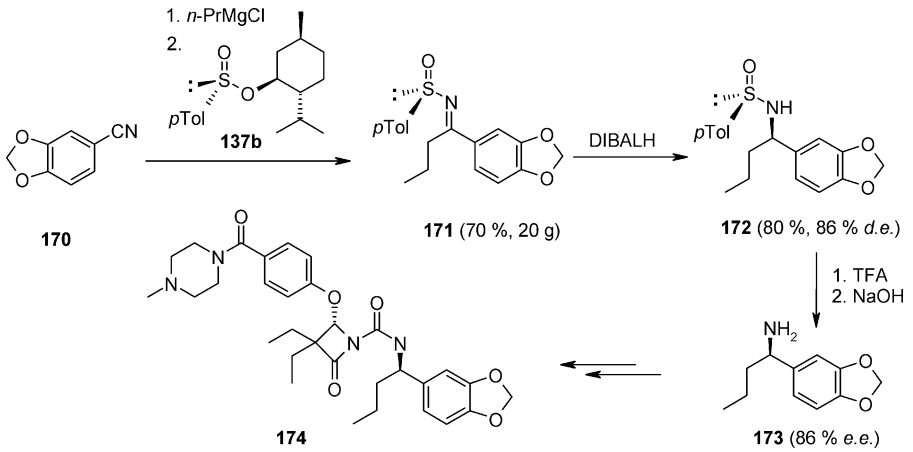
Scheme 64. Synthesis of Planar Chiral Mono- and Diphosphine Ligands[87]



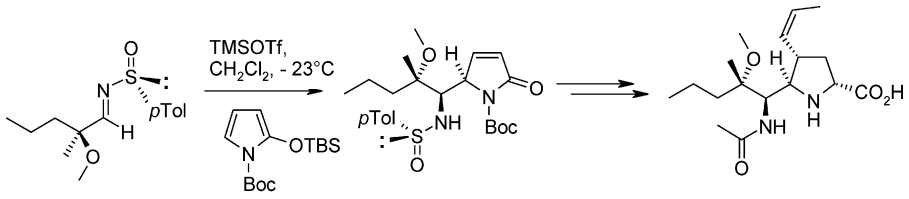
Scheme 65. Synthesis of Chiral Sulfinimines According to Davis et al.[89d]



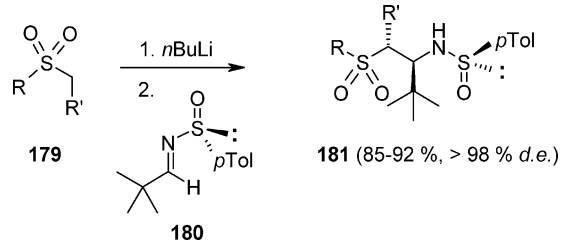
Scheme 66. Reduction of Chiral Sulfinimines According to Storace et al.[91]



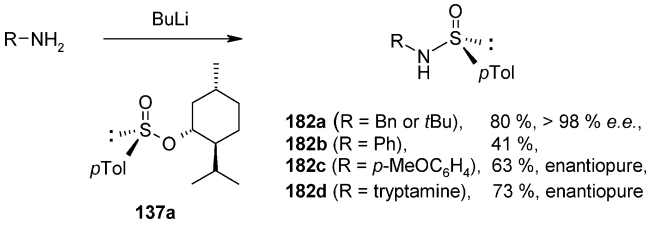
Scheme 67. Synthesis of Antiinfluenza Compound A-315675 (178)[92]



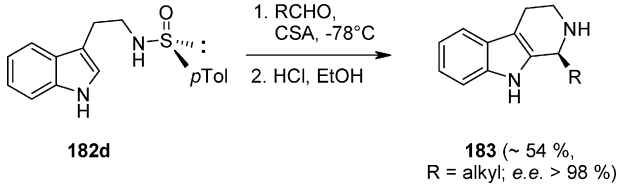
Scheme 68. Addition of Sulfonyl Anions to Sulfinimines 180 According to Velazquez et al.[93]



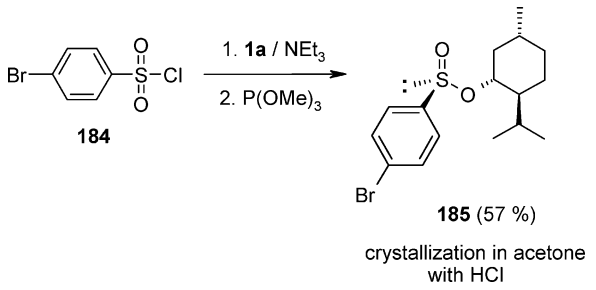
Scheme 69. Addition of Lithiated Amines to Andersen's Reagent[94]



Scheme 70. Pictet−Spengler Reaction According to Koomen et al.[94d]



Scheme 71. Synthesis of Menthyl *p*-Bromobenzenesulfinate (185) According to Naso et al.[95]



as illustrated in Scheme 72.[95b,96] The first substituent is introduced pursuant to the standard protocol accompanied by the loss of menthol. In the second step, the *p*-bromophenyl substituent acts as a leaving group and is easily replaced by aliphatic Grignard reagents.

Remarkably, both steps proceed with very good stereoselectivity and a double inversion of configuration at the sulfur center. Regarding the excellent yields, this approach paves the way for the synthesis of enantiopure dialkylsulfoxides **187**.

Plainly, the bromine atom can be used for further functionalization, as has been demonstrated by Gallina et al. (see Scheme 73).[97] For their synthesis of metalloproteinase inhibitor **190**, they transferred Davis' sulfinimine approach (see Scheme 65) onto *p*-bromoderivative **185**. Subsequent stereoselective addition of lithium diethylphosphite affords the phosphonate **189** as single isomer after chromatographic workup in good yield over three steps.

Oxidation of the sulfur, consecutive Suzuki-coupling with *p*-methoxyphenyl boronic acid, and acid hydrolysis gives **190** in enantiopure form. This sequence benefits from the availability of both enantiomers of menthol, for both enantiomers of **190** were prepared and crystallized as complexes of the respective metalloproteinase. Therefore, their different binding properties and interactions with respect to chirality could be studied in detail.

2.6. Menthyl Chloride

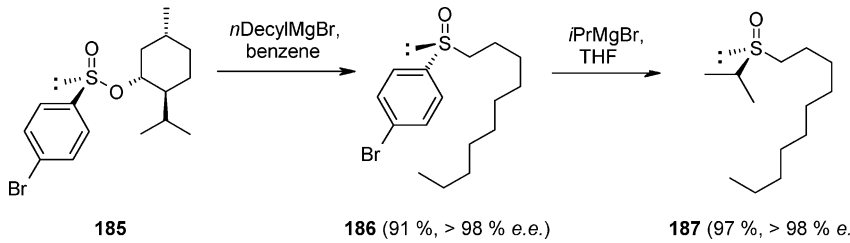
2.6.1. Synthesis

If the hydroxyl group in the menthyl scaffold **1a** is replaced with a chlorine atom in an S_N-fashion, the stereochemical outcome of this reaction allows two possibilities: either substitution under retention resulting in menthyl chloride (**191b**)[98] or reaction with simultaneous inversion of the configuration yielding neomenthyl chloride (**191a**)[99] (see Scheme 74). Both protocols have been established on a preparative scale since the 1950s.

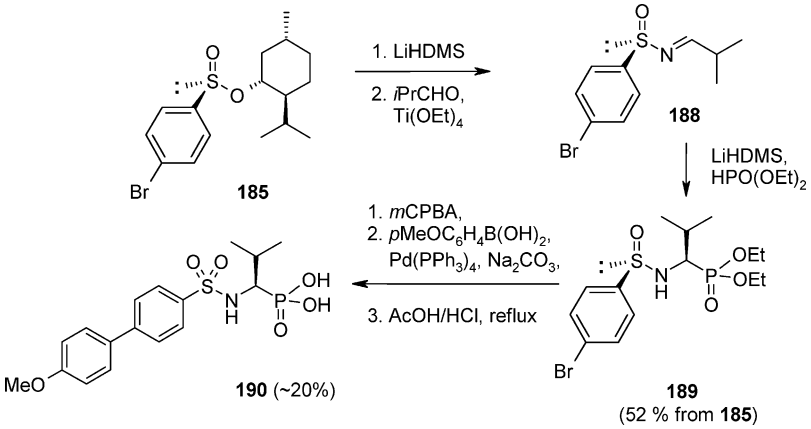
2.6.2. Menthyl Diphenylphosphine

Most frequently, the menthyl chloride (**191b**) serves as a precursor for the corresponding Grignard reagent,[100] which is configurationally stable[100a] and was therefore em-

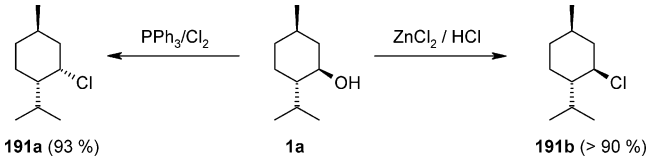
Scheme 72. Double Replacement Sequence According to Naso et al.[95b,96]



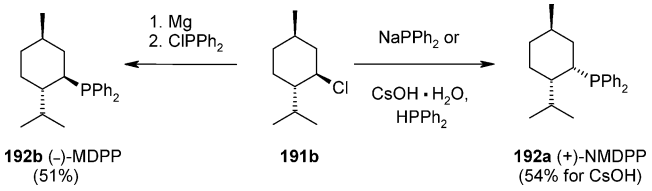
Scheme 73. Synthesis of Enantiopure Matrix Metalloproteinase Inhibitor 190[97]



Scheme 74. Synthesis of Menthyl Chloride (191b)[98] and Neomenthyl Chloride (191a)[99]



Scheme 75. Synthesis of Neomenthyl and Menthyl Diphenylphosphines (192a and 192b)[101]



ployed in the synthesis of menthyl diphenylphosphine (**192b**),[101b] a chiral tertiary monophosphine ligand (see Scheme 75).[101]

Starting from the same menthyl chloride (**191b**), the diastereomeric monophosphine ligand **192a** is accessible via nucleophilic substitution of the halogen. The fairly cumber-

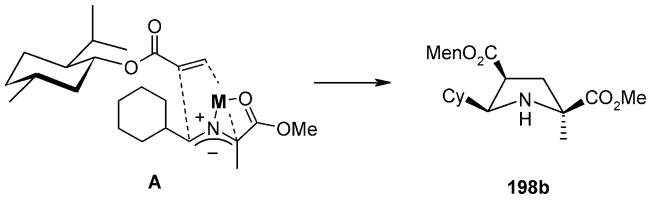
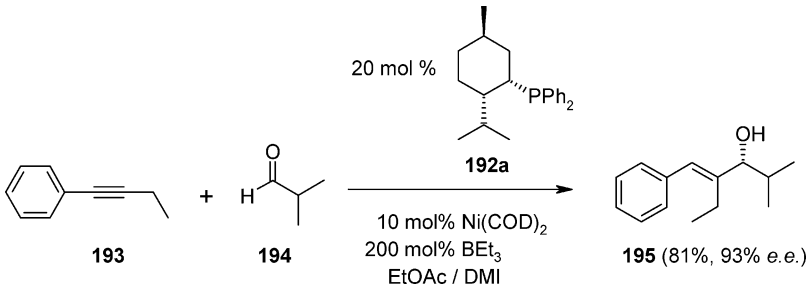
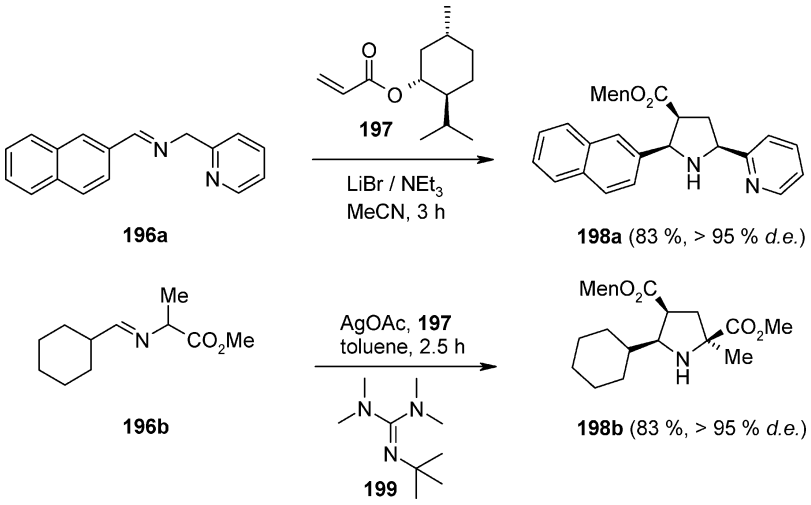


Figure 3. Transition state for the formation of **198b** according to Grigg et al.[110]

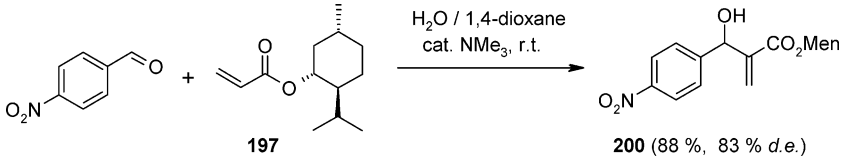
Scheme 76. Asymmetric Reductive Coupling Using (+)-NMDPP According to Jamison et al.[104]



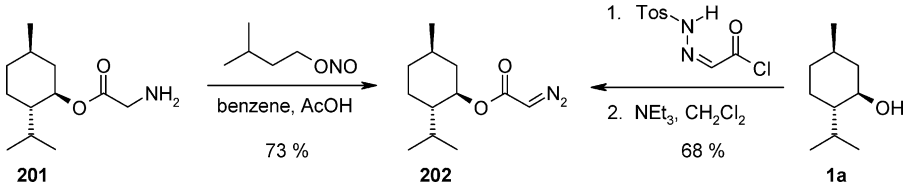
Scheme 77. Stereoselective Synthesis of Different Pyrrolidines According to Grigg et al.[110]



Scheme 78. Asymmetric Baylis-Hillmann Reaction in Aqueous Media According to Tang et al.[111]



Scheme 79. Synthesis of Menthyl Diazoacetate (202)[112]



some original protocol was recently improved by the use of cesium bases.[101d]

Although **192a** is a commercially available chiral monophosphine ligand, its use in organic synthesis is limited: both isomers have been utilized for hydrogenation,[102] hydrosilylation,[103a] and hydroesterification reactions.[103b] Recently, their scope of application was extended to the nickel-catalyzed reductive coupling of alkynes **193** with aldehydes **194** as illustrated in Scheme 76.[104]

Using equal volumes of 1,3-dimethylimidazolinone (DMI) and ethyl acetate as solvent, the catalytic system affords trisubstituted allylic alcohols **195** corresponding to the exclusive *cis*-addition to the alkyne in excellent regioselectivity and in 93% ee.

2.7. Menthyl Acrylate

2.7.1. Synthesis

Menthyl acrylate (**197**) is easily prepared via transesterification of acrylic acid methylester,[105] conversion of acryloyl chloride,[106] HCl-elimination from menthyl β-chloropropionate,[107] or triphenylphosphine-catalyzed reaction of maleic anhydride with menthol.[108]

2.7.2. Applications

Menthyl acrylate was widely applied in Lewis acid promoted Diels−Alder reactions as chiral dienophile but constantly was surpassed by its menthone-derived sibling 8-phenylmenthol in terms of selectivity.[3,109]

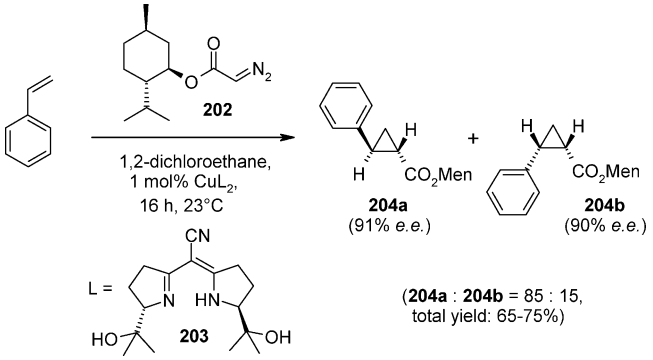
Better results were achieved by Grigg et al.[110] using a 1,3-dipolar cycloaddition approach for the construction of substituted pyrrolidines **198** (see Scheme 77) starting from azomethine ylides derived from imines **196**.

The carefully chosen combination of base and metal salt afforded a set of sterically crowded heterocycles **198**, with guanidine base **199** commonly giving the best yields. According to Grigg et al.,[110] a stereochemical model of the transition state is depicted in Figure 3. The isopropyl group of the menthyl moiety shields the C(α)-*Si*-face of the acrylate, which reacts out of a *s-cis* conformation.

An example for asymmetric Baylis-Hillman reactions was presented by Tang et al.[111] (see Scheme 78). Addition of *p*-nitrobenzaldehyde to menthyl acrylate in aqueous dioxane gave the allylic alcohol **200** with good yield and selectivity.

In case the *m*-nitroaldehyde is employed, the selectivity rises to 99% de, albeit at the expense of the chemical yield, which is decreased to 45%.

Scheme 80. Copper-Catalyzed Cyclopropanation According to Pfaltz et al.[113a]



2.8. Menthyl Diazoacetate

2.8.1. Synthesis

Two different procedures have been reported in detail for a synthesis on a multigram scale (see Scheme 79): menthyl glycinate (**201**), which is easily accessible via direct esterification of menthol with glycine,[112a] is diazotized with isoamyl nitrite. After chromatography, menthyl diazoacetate (**202**) is obtained as yellow crystals in good yield.

An alternative one-pot protocol was described by Landgrebe and co-workers:[112c] esterification of menthol with glyoxylchloride tosylhydrazone and subsequent addition of triethylamine gives the diazoester **202** in comparable yield.

2.8.2. Applications

The most popular application of chiral diazoester **202** is the asymmetric Cu-,[113] Rh-,[114] or Ru-mediated[115] cyclopropanation reaction. Because of generally convenient chromatographic separations often found for each of the cyclopropane diastereomers **204**, (+)- and (−)-menthyl diazoacetate have been commonly used to assess diastereoselection in catalytic systems. This is exemplified in Scheme 80 for a copper complex with two semicorrine ligands **203** invented by Pfaltz et al.[113a] in 1986.

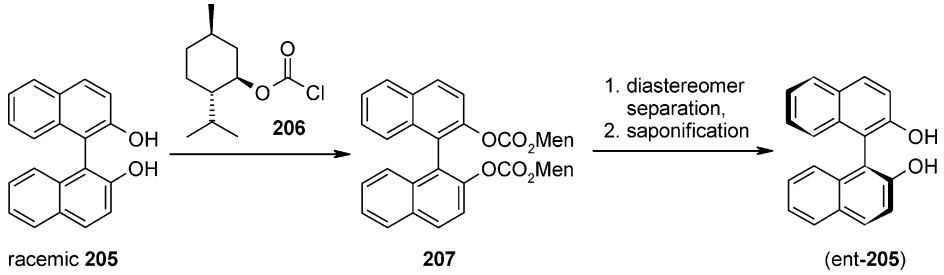
In the case that (+)-menthol is employed for **202**, the selectivity of the catalyst could be clearly improved, and **204** is received in an excellent 95−97% ee optical purity. Those results for the cyclopropanation of styrene were unmatched in 1986 and remain impressive even twenty years later.

2.9. Menthyl Chloroformate

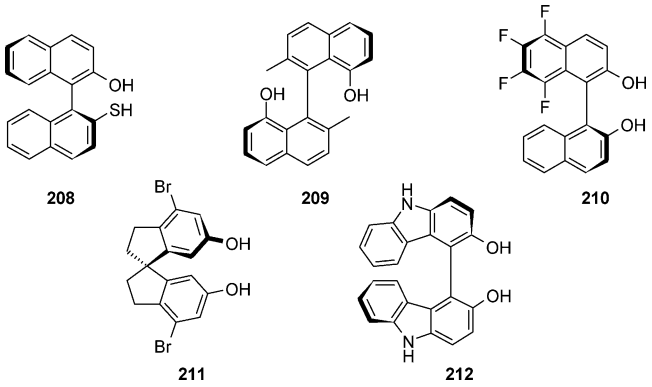
2.9.1. Synthesis

Menthyl chloroformate (**206**) is most commonly synthesized via a simple reaction of menthol with phosgene in the

Scheme 81. Resolution of Binaphthyls According to De Lucchi et al.[118a]



Scheme 82. Variety of Binol Derivatives 208−212 Resolved via the Menthyl Chloroformate Protocol[118,117c]



presence of an amine base.[116] Because of the high toxicity and volatility of phosgene, triphosgene $OC(OCCl_3)_2$ is frequently used as a replacement.[117]

2.9.2. Resolution of Binaphthyls

Menthyl chloroformate is almost exclusively used to derivatize racemic alcohols or amines in order to resolve their enantiomeric counterparts. One especially successful strategy is outlined in Scheme 81.

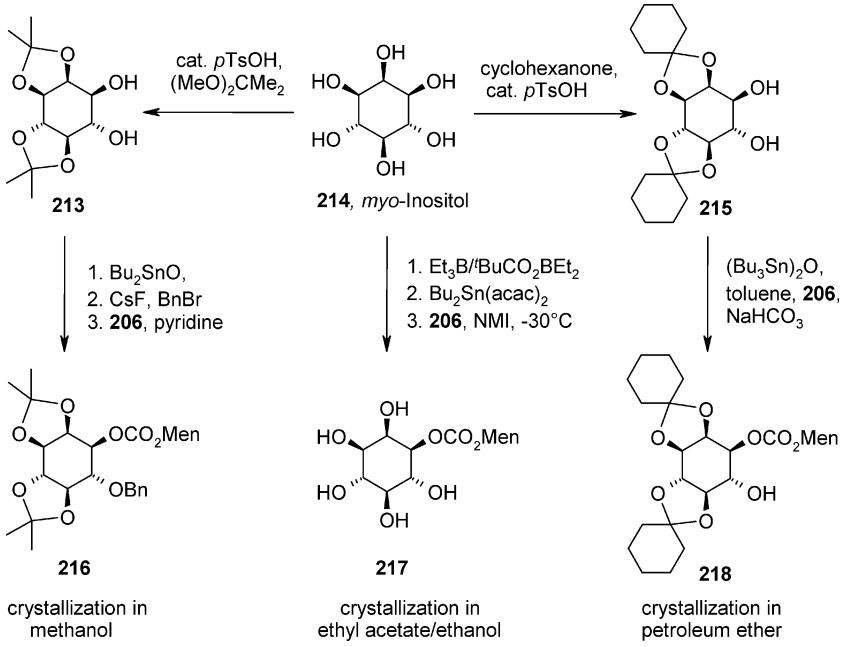
Axially chiral diols **205** can be easily converted into their bis-menthyl carbonates **207**, which generally exhibit a high difference in crystallinity. Diastereomer separation is either achieved via simple crystallization or in some cases through chromatographic methods. Cleavage of the terpene auxiliary is a standard operation, employing KOH or $LiAlH_4$. The ease and applicability of this protocol is reflected in Scheme 82, which shows very recent examples of effective resolutions.

2.9.3. Resolution of myo-Inositol

A further example is illustrated in Scheme 83: *myo*-inositol (**214**) is a *meso*-hexahydroxycyclohexane, occurring in nature in its tris-phosphorylated form, namely, *myo*-inositol 1,4,5-tris-phosphate, playing a major role in transmembrane cell signaling. Any functionalization starting from *myo*-inositol (**214**) to corresponding derivatives **216**−**218** has to master the challenges of regio- and enantioselectivity, which becomes obvious in all three different *myo*-inositol-scaffold modifications presented by Schmidt,[119c,d,e] Bittman,[119f,g] or Martin-Lomas.[119a,b]

All approaches consistently make use of menthyl chloroformate (**206**) to resolve the racemic mixtures, and all diastereomeric menthyl carbonates are formed at the C-1 position. Bittman's and Schmidt's syntheses start with a double acetalisation of *myo*-inositol (**214**) giving bis-protected diols **213** and **215**, respectively. In a likewise tin-mediated fashion, only one of the two hydroxy moieties is transformed into the menthyl carbonate giving **218** in a controlled manner. Compound **216** resulted from the initial tin-mediated benzylation followed by reaction with **206**. Starting from the unprotected *myo*-inositol (**214**), Martin-Lomas et al. effected conversion into the monosubstituted carbonate **217** directly via a perborylation/transmetallation

Scheme 83. Different Synthetic Routes to an Enantiopure *myo*-Inositol-scaffold[119]



sequence. In all cases, diastereomerically pure menthyl carbonates **216**−**218** were achieved via crystallization from different solvents as is indicated in Scheme 83. Schmidt et al. even mention that scale-up of this convenient resolution process resulted in the manufacture of 50 g quantities of **218**. The enantiomers of **216** and **218** were prepared in the same way but employing the respective optical antipode of menthyl chloroformate.

3. Conclusion

As menthol has been known to mankind since antiquity and is among the most readily available compounds from the "chiral pool", its use in synthetic organic chemistry is prevalent. Because of its benefiting properties as a nontoxic material which is highly crystalline, cheap, environmentally friendly, and most of all on-hand in both enantiomeric configurations in bulk quantities, almost any discipline of preparative chemistry availed from its advantages.

With asymmetric synthesis being considered one of the major frontiers in chemistry, further contributions from academic and industrial research to this field have to be expected. One can conclude without overstatement that menthol, seen on a historical scale, is one of those exclusive molecules that helped to shape asymmetric organic synthesis and is likely to do so in the future.

4. References

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CR068409F