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FEATURE ARTICLE

Menthone and *p*-menthyl-3-carboxaldehyde as chiral auxiliaries

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Two chiral auxiliaries and the role they play in the preparation of chiral carbonyl compounds and heterocyclic compounds are presented. Key reactions include S_N2' displacements, Mitsunobu with hydrazoic acid, and 3,3-sigmatropic rearrangements. One of the auxiliaries serves many functions and is removed either by oxidative cleavage or RCM reaction.

Introduction

Many chiral enolates were designed and developed during the Golden Age of chiral auxiliaries (Fig. 1).¹ Names like Evans, Oppolzer, Brown, Corey, Helmchen, and, of course, Meyers resonated in almost every classroom where advanced organic chemistry was taught in the 1980's and 1990's. Some still do

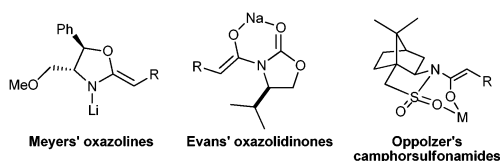


Fig. 1 Examples of chiral enolates used in alkylation reactions.

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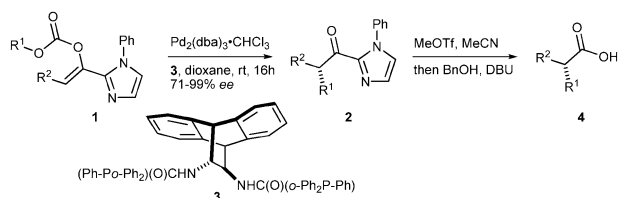
Claude Spino received a BSc from Université de Montréal (1983) and moved to Vancouver (UBC) to complete his PhD degree (L. Weiler, 1988). His doctorate work concerned the synthesis of polyether antibiotic ionomycin. After a post-doctoral stay in Sherbrooke (1988–1990), the University of Victoria hired him as an assistant professor where he started his career working on the synthesis of the anti-cancer quassinoids. He moved back to the Université de Sherbrooke

in 1995 where he is now full professor. His research interests are varied and include total syntheses of natural products, the development of synthetic methodologies, and mechanistic studies.

today. More recently, better designed systems led to improvements in the reactivity and selectivity of chiral enolates, but these were few.² The advent of new and ever more enantioselective catalytic reactions seemed to signal the imminent end of the era of the covalently bound auxiliary for that chemistry, and perhaps many others. It is beyond the scope of the present article to review the field of asymmetric alkylation, but Trost's latest methodology for the catalytic asymmetric decarbonylative alkylation of carbonates **1** serves as an example of the state of affairs in this field (Scheme 1).³

However, the literature on the synthesis of complex natural products tells a different story. As a case in point, just browsing the recent literature reveals a recent synthetic approach by Crimmins and coworkers toward the complex natural product (–)-brevenal, where at least four chiral enolates are used to prepare complex chiral synthetic intermediates.⁴ There may be many reasons why, but some I may suggest include the predictability, dependability, reproducibility, and wide substrate scope covalently-bound chiral auxiliaries offer. These features can be crucial in a synthesis of a complex target.

Yet, the chemistry of enolates has severe limitations: enolates are usually not very reactive (practically, only primary alkyl halides may be used as carbon sources), self-condensation can be a problem, and they may be generated as mixtures of geometric isomers or perhaps only one geometry of the enolate is available. Fortunately, an alternative exists. This account will focus on two of our own auxiliaries, namely menthone and *p*-menthane-3-carboxaldehyde, and briefly describe related systems. Taken together, they offer an excellent substitute to and nicely complement the chemistry of chiral enolates.



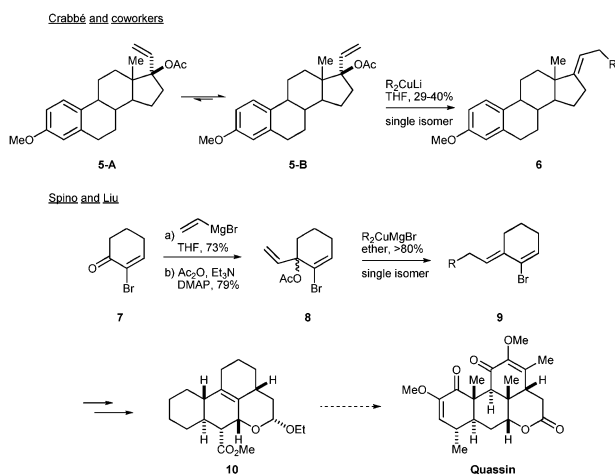
Scheme 1 Trost's latest catalytic asymmetric decarbonylative alkylation.

Alkylations to make 3° chiral carbons

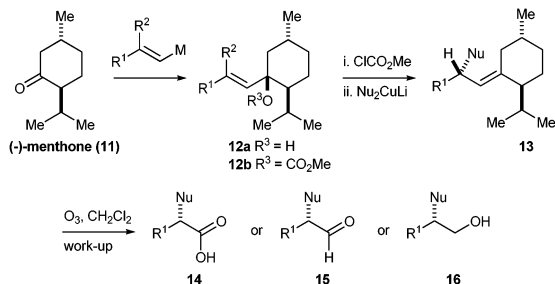
Inspired by the early work of Crabbé and co-workers on the steric course of cuprate additions to allylic acetate,^{5,6} we utilised this stereoselective S_N2' displacement as part of a synthetic approach⁷ to the cytotoxic quassinoids⁸ (Scheme 2). Only one geometrical isomer of the alkene product is formed because of the steric congestion experienced by one of the reactive conformers of the starting allylic acetates (e.g. conformer **5-B** in Scheme 2).

Thanks to the work of Harlan Goering⁹ and others,¹⁰ we became aware of the propensity of cuprate reagents to add in a stereospecific manner *anti* to the leaving group. Putting these two concepts together, we surmised that adding a substituted vinyl fragment to a chiral ketone, in lieu of **7**, might allow us to develop an alternative to existing methodologies to prepare α -chiral carbonyl compounds.

Scheme 3 depicts our initial work towards this goal.¹¹ Menthone (**11**) is a monoterpene commercially available in both enantiomeric forms.¹² A few other commercially available chiral ketones, such as camphor, were tested but none of them would react with vinyl lithium reagents as selectively or in good a yield as menthone. Activating the resulting alcohol **12a** as a carbonate (**12b**) allowed the stereospecific additions of cuprate reagents to give a single stereo- and geometric isomer of **13**. Only carbonates **12b** where R² = H would lead to product **13**. Subsequent ozonolysis of



Scheme 2 Early work on the preparation of geometrically defined exocyclic alkenes.



Scheme 3 Four steps sequence to chiral acids, aldehydes or hydroxymethyls.

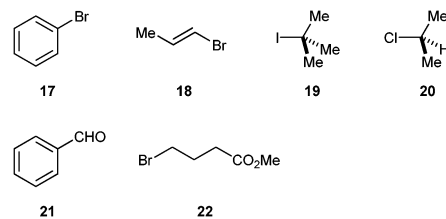


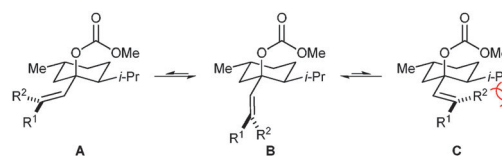
Fig. 2 Usable substrates in either methodology.

the exocyclic alkene in **13** gave good yields of either the carboxylic acid **14**, the aldehyde **15**, or the hydroxymethyl compound **16**, depending on the work-up conditions. Two features of this sequence of reactions are immediately apparent: (a) the products **14–16** are identical to those obtained by the alkylation of chiral enolates; (b) the chiral auxiliary is attached to the nucleophile in the alkylation of chiral enolates whereas our chiral auxiliary bears the electrophile. So, in an ‘umpolung’ sense, the two approaches complement each other: the electrophiles **17–20** (Fig. 2) are easily converted to cuprate reagents and give, upon addition to **12b**, the corresponding product **13** in good yields, but they cannot usually be used as electrophiles for the alkylation of chiral enolates; on the other hand, electrophiles **21** and **22** are productive in the alkylation of chiral enolates but their conversion to cuprate reagents is implausible or impractical.

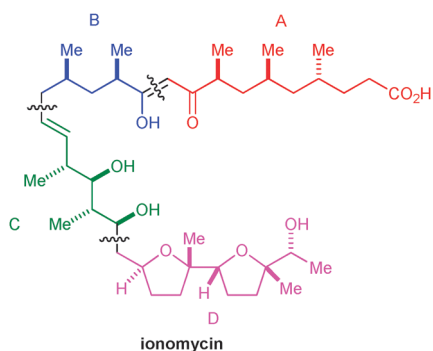
Knochel and co-workers have developed conditions to add cuprate reagents derived from organozinc compounds to allylic phosphates,¹³ or pentafluorobenzoates.¹⁴ Organozinc reagents are tolerant of many reactive functional groups such as esters or nitriles. Although we have not yet used organozincs in our methodology, it could potentially increase its scope.

The strategy depicted in Scheme 3 compares favourably to the more classical alkylation of chiral enolates¹⁵ in that most cuprate additions on **12b** gave products **13** with >99% de. The large energy difference between the reactive conformers **A** and **C** (R² = H, > 4 kcal mol⁻¹) together with the high stereospecificity of cuprate S_N2' additions¹⁶ are responsible for the observed stereoselectivity in the transformation of **12b** to **13** (Scheme 4). While conformer **B** may be the most stable, it is unreactive because the orbitals of the π -system are not aligned with the σ^* orbital of the leaving group. Ozonolysis of the double bond releases the desired carbonyl product **14–16** with no detectable racemization, along with the recyclable chiral auxiliary. By comparison, the hydrolysis of many chiral amide auxiliaries must be performed under harsh conditions where racemization becomes an issue.¹⁵ Moreover, compounds **14** and **15** are often produced indirectly by oxidation of the hydroxymethyl compound **16**.

As a case in point, we prepared the commercial behemoth (+)-ibuprofen (*ent*-**14**, Nu = 4-(*i*-Bu)Ph, R¹ = Me) in



Scheme 4 Three conformations of **12b**.



ionomycin

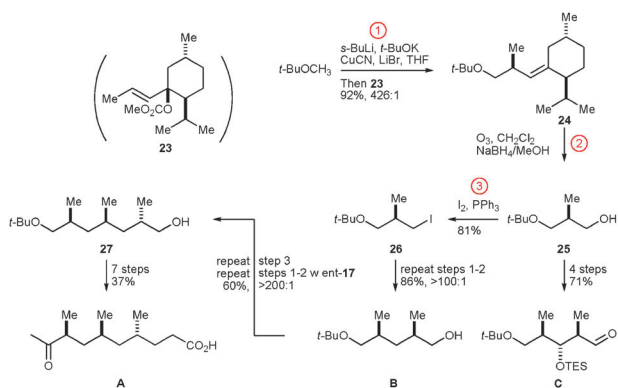
Fig. 3 Ionomycin and its disconnections into fragments A–D.

enantiomerically pure form in 4 steps and 60% overall yield from (+)-menthone, *trans*-bromopropene, and 4-*i*-BuPhBr.¹⁷

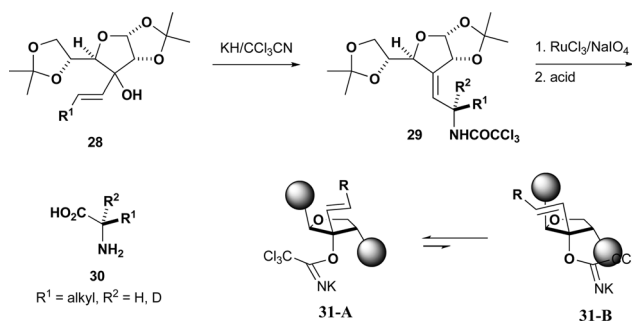
High stereoselectivity in each reaction of a sequence becomes critically important when using the sequence in an iterative approach to the synthesis of a complex natural product. We have prepared three of the four fragments of the polyether ionophore ionomycin¹⁸ (Fig. 3) using a stereo-divergent and iterative approach that makes use of a three-step synthetic sequence as well as pseudosymmetry present in ionomycin (Scheme 5).¹⁹ At each iteration, we could barely detect the second diastereomer formed such that after three iterations, we obtained an essentially diastereomerically pure fragment A of ionomycin.²⁰ The other two fragments B and C were made from intermediates along the synthetic path to fragment A, thus allowing us to keep the number of steps in the synthesis down.

Other research groups have developed similar systems. The first was the research group of Kakinuma and coworkers, who developed a chiral ketone derived from D-glucose and to which they added vinylmetals stereoselectively, to procure **28** (Scheme 6). They then performed rearrangement reactions to yield **29** and, after oxidative cleavage, chiral amino acids **30**.²¹ No displacement reaction has been reported for this system but we believe, based on our own experience, that it would not perform well because of the inherent steric crowding on both sides of the central sugar moiety (*cf.* **31-A** and **31-B** and the discussion concerning the three conformations **A–C** in Scheme 4).

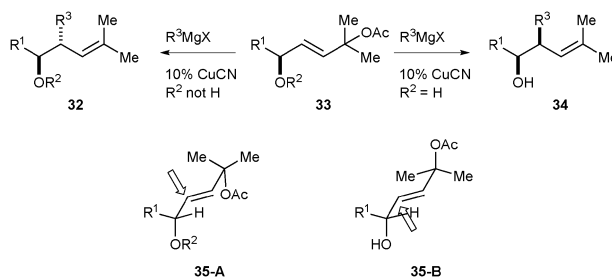
Belelie and Chong reported a highly S_N2'-selective method based on the displacement by cuprates of allylic phosphates.²²



Scheme 5 Synthesis of 3 fragments (A–C) of ionomycin.



Scheme 6 Kakinuma's sugar-based auxiliary system.



Scheme 7 Chong & Belelie's stereocontrolled synthesis of chiral non-racemic homoallylic alcohols.

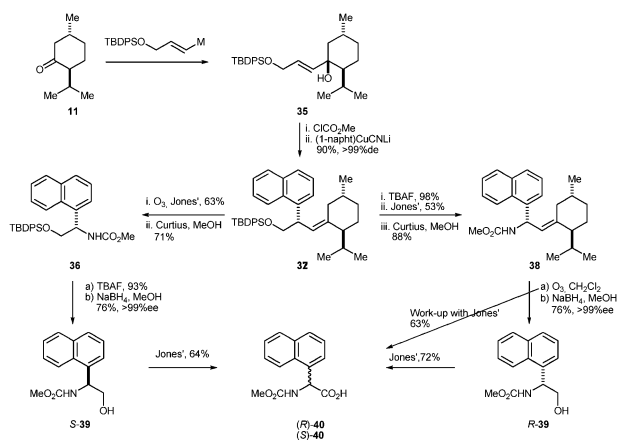
In their first generation system, the initial non-racemic allylic alcohols were obtained by kinetic resolution. Later, α -oxy-substituted allylic acetates **33** gave them alkylation products **32** or **34**, depending on the nature of the oxy-substituent (Scheme 7).²² Ethers **33** ($R^2 \neq H$) gave the addition products **32** from the A^{1,3}-strain minimized conformer **33-A**, whereas alcohols **33** ($R^2 = H$) delivered the cuprate reagent on the lower face of the alkene in conformer **33-B**. After oxidative cleavage of the double bond, compounds **32** or **34** gave aldol-type products.

More recently, Bäckvall and coworkers have used a chemoenzymatic dynamic kinetic resolution to effect the synthesis of chiral allylic esters and reported using the latter in copper-catalyzed allylic substitution reactions to produce α -chiral carboxylic acids.²³ Many groups have also contributed to the general transformation of an allylic leaving group by cuprate reagents.^{16,24}

Installing a protected hydroxymethyl substituent, as a masked carboxylic acid, on the vinyl portion allowed us to devise a simple stereodivergent way to make chiral amino acids and oxazolidinones of high enantiomeric purity.²⁵ For example, from a single intermediate **37**, which itself can be prepared in either enantiomeric form, one can construct both enantiomers of the targeted amino acid **40** simply by changing the order of reactions in the sequence shown (Scheme 8).

Alkylations to make 4° chiral carbons

One of the first extensions that we wanted to develop for this system was the construction of all-carbon quaternary stereocenters. There are very few general methods to make them with good stereocontrol.²⁶ However, the menthone system, as described above, is incapable of generating quaternary stereocenters. The reason is that conformers **A** or **C**

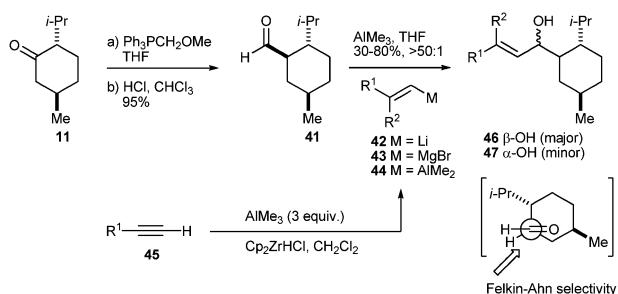


Scheme 8 Stereodivergent synthesis of (*R*)- and (*S*)-amino acid **40**.

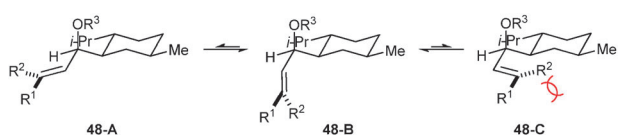
($R^2 \neq H$ in Scheme 4) are too high in energy and are not available in sufficient concentration for the reaction to take place. Only conformer **B** is available to this type of substrates but it is unreactive towards cuprate reagents.

It should be reasonably easy to alleviate this problem by choosing an aldehyde, like **41**, in lieu of a ketone as the chiral auxiliary (Scheme 9). The presence of a hydrogen on the carbinol carbon should make the required conformation **48-A** energetically attainable for cuprate addition when $R^2 \neq H$ (Scheme 10), while retaining sufficient difference in energy between the two reactive conformations **48-A** and **48-C**. The real question is: why have we chosen *p*-menthyl-3-carboxaldehyde **41**? One could think of a number of other aldehydes that may appear more appropriate. Yet, the chosen auxiliary aldehyde had to meet several criteria: (a) be cheaply available in both enantiomeric series; (b) add vinylmetal diastereoselectively; (c) help in ensuring the proper regioselectivity of the subsequent cuprate addition (S_N2 vs. S_N2' additions); (d) be easily removed; (e) be recoverable.

Of course, one cannot at first glance predict that a given structure will fulfill all these promises. Aldehyde **41** was prepared in two easy steps from menthone and happened to be one of the first aldehydes we looked at. Quite frankly, I was



Scheme 9 Preparation and addition reaction of chiral auxiliary **41**.



Scheme 10 Three conformations of the ester **48**.

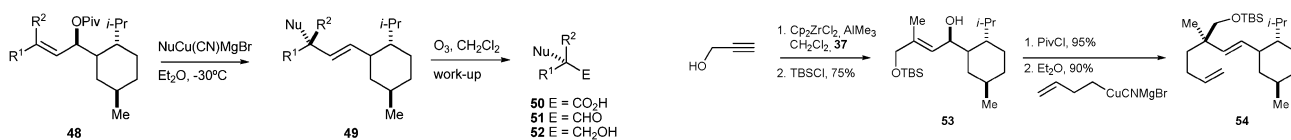
personally very doubtful that vinylmetals would add stereoselectively to aldehyde **41** and our first investigations toward this goal proved me right. Using vinylolithium reagents **42** or vinyl Grignard reagents **43**, stereoselectivities in the range of 1.5 : 1 (**46** : **47**) were obtained. Yet, constructing all-carbon quaternary stereocenters require trisubstituted vinylmetals, where R^1 and R^2 are alkyls or aryls. One of the easiest method to achieve this is Negishi's zirconium-catalyzed carboalumination²⁷ of alkynes **45**. Against my own advice,²⁸ Christian Beaulieu added *p*-menthyl-3-carboxaldehyde **41** directly to the mixture obtained from the carboalumination of *n*-hexyne (**45a**, $R^1 = n\text{-Bu}$) and procured 80% yield of the corresponding two alcohols **46a** and **47a** ($R^1 = n\text{-Bu}$, $R^2 = \text{Me}$) in a 20 : 1 ratio.²⁹ The major product **46a** was the result of a Felkin–Anh addition to aldehyde **41** (Scheme 9).

For a while, we believed that the purported vinylalane intermediate **44a**, obtained from the carboalumination reaction of **45a**, was responsible for this dramatic increase in stereoselectivity.³⁰ However, serendipitous removal of excess trimethylaluminum by evaporation soon revealed that it was responsible for the high stereoselectivity observed. Could excess AlMe_3 also increase the stereoselectivity of other vinylmetals? Indeed, it could. Addition of vinylolithium in the presence of a catalytic amount of AlMe_3 (10%) increased the stereoselectivities of up to 10 : 1. Addition of an excess AlMe_3 (best results with 2.5 equiv.) brought the level of stereoselectivity to a whopping 100 : 1.³¹ Strangely, the use of exactly 1 equiv. of AlMe_3 leads to a sluggish and incomplete reaction. We have yet to definitely explain this phenomenon but we believe that the 'ate' complex formed between the vinylolithium and AlMe_3 is actually unreactive. The reaction would proceed from the small amount of free vinylolithium and AlMe_3 present in the solution thanks to an equilibrium between the 'ate' complex and the free species. Free AlMe_3 acts as a Lewis acid and strongly activates the carbonyl towards addition of the vinylolithium as well as provide an increase in stereoselectivity according to the Heathcock model.³² When 1 equiv. of each species is used, their effective concentration may be too low and the reaction becomes very slow.

We demonstrated that AlMe_3 increased the Felkin–Anh selectivity of the addition of vinylolithium reagents to many other α -chiral aldehydes.³¹ Cerium trichloride will also somewhat increase the stereoselectivity of addition of alkynyl-lithium reagents to α -chiral aldehydes.³³

At this stage, we could have looked more extensively for other aldehydes that may not require an additive such as AlMe_3 to yield diastereomerically pure allylic alcohols like **46**. α -Alkoxyaldehydes and Garner's aldehyde³⁴ were considered, but the presence of heteroatoms on the chiral auxiliary could be detrimental to the overall sequence since we used such reactants as cuprates and ozone in it. Other aldehydes like 2-phenylpropanal were tested but none possessed all the advantages of **41**, as it became clear later on.

For a start, we had little problem optimizing the coveted cuprate addition onto pivalate ester **48** to give **49**, as the chiral auxiliary proved bulky enough to prevent products from S_N2 reactions (Scheme 11). Typical examples are given in Table 1 (entries 1–7). A pivalate ester is essential for high



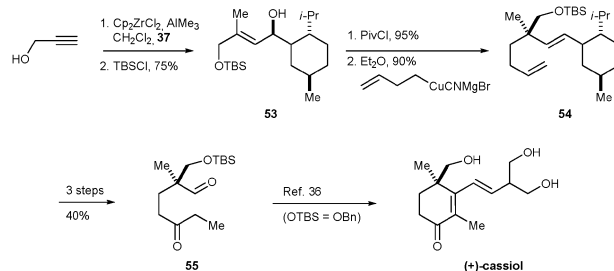
Scheme 11 Addition of cuprates to pivalate ester **48**.

regioselectivity, which we attribute to enhanced steric effects. Monoalkylcyanocuprates give higher yields than other types of cuprates, which is just as well since only one equivalent of the alkyl fragment is required to make them, as opposed to dialkylcuprate reagents. Because a quaternary carbon is being formed in this reaction, less reactive or bulky cuprate reagents such as *t*-BuCuCNMgBr and PhCuCNMgBr are not suitable (entries 9 and 10).³⁵ Also, if a *t*-Bu group is already present on the alkene, the addition reaction fails (entry 8). That would have created two adjacent quaternary carbons. The oxidative cleavage of the carboxymethyl moiety was achieved much the same way as per menthone to yield acids **50**, aldehydes **51**, or hydroxymethyl compounds **52**, all bearing an all-carbon α -quaternary center. Separation of the desired product from the recovered chiral auxiliary was tricky in cases where all substituents in **50–52** (R^1 , R^2 , and Nu) are lipophilic alkyl groups.

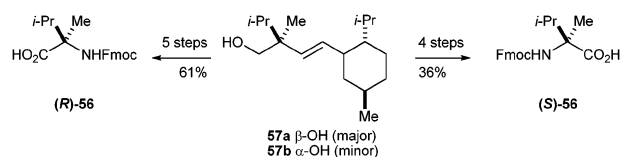
We performed a formal synthesis of the anti-ulcer (+)-cassiol³⁶ to demonstrate the usefulness of this method (Scheme 12). Compound **55**, an enantiomerically pure (>99%ee) derivative of Taber's intermediate was obtained in only seven steps from structurally very simple starting materials.³⁷

The strategy for the stereodivergent synthesis of both enantiomers of α -amino acids from a single intermediate (as was described for menthone in Scheme 4) could be again implemented, but this time to make α,α -dialkylated α -amino acids. Scheme 13 depicts this strategy for the synthesis of both enantiomers of α -methyl valine **56**.³⁸ α,α -Dialkylated α -amino acids are prized building blocks for unnatural peptides and peptoids as a means to controlling their secondary and tertiary structures and decreasing their metabolism rate.³⁹

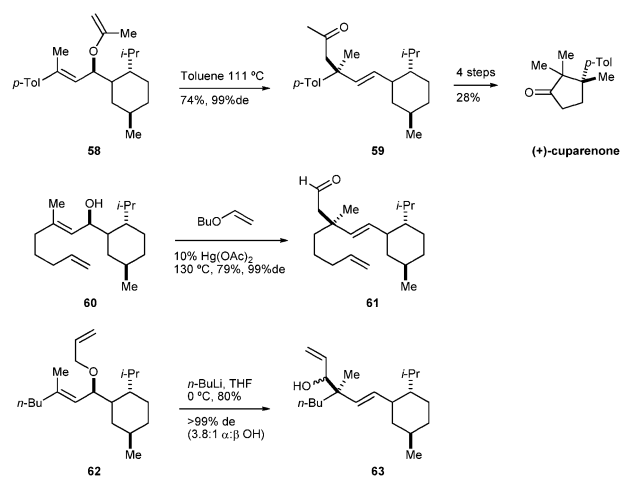
Sigmatropic rearrangements are also viable to make all-carbon quaternary stereocenters on our system. Claisen and 2,3-Wittig rearrangements have been rarely used to make all-carbon quaternary stereocenters.⁴⁰ Both types of rearrangement function very well on our system at temperatures that are surprisingly low considering all-carbon quaternary centers are produced (Scheme 14).³⁵ The menthyl nucleus is



Scheme 12 Formal synthesis of (+)-cassiol.



Scheme 13 Stereodivergent synthesis of (*R*)- and (*S*)- α -methylvaline **56**.



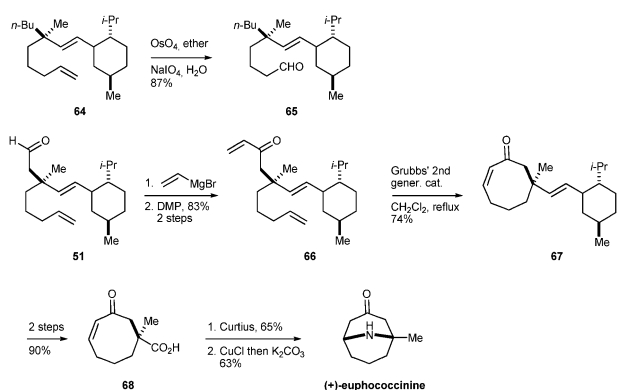
Scheme 14 Sigmatropic rearrangement reactions.

not innocent in that it provides a steric decompression factor to ease the rearrangements. This phenomenon will be displayed in a more dramatic fashion in the sigmatropic rearrangement of an azide (*vide infra*). We prepared the archetypal molecule (+)-cuparenone in >99%ee from the Claisen rearrangement of enol ether **58** to **59** (Scheme 14).⁴¹ Claisen rearrangement product **61** was used in the total synthesis of an alkaloid

Table 1 Stereoselectivities in the additions of cuprate reagents to esters **48**

Entry	R^1	R^2	Nu	Prd	Yield ^a (%)	%de ^b
1	<i>c</i> -Hex	Me	<i>i</i> -Pr	49a	95	> 98
2	PhCH ₂	Me	<i>i</i> -Pr	49b	92	> 98
3	Ph	Me	<i>i</i> -Pr	49c	90	91
4	-(CH ₂) ₃ OTBS	Me	Et	49d	89	> 98
5	-(CH ₂) ₃ OTBS	Me	H ₂ C=CH(CH ₂) ₂ -	49e	82	> 98
6	<i>m</i> -MeOPh	CH ₂ OH	Et	49f	86	> 98
7	<i>n</i> -Bu	Me	<i>n</i> -C ₇ H ₁₅	49g	90	> 95
8	<i>t</i> -Bu	CH ₂ OH	Et	49h	0	—
9	<i>n</i> -Bu	Me	<i>t</i> -Bu	49i	0	—
10	<i>n</i> -Bu	Me	Ph	49j	0	—

^a Only one regioisomer observed. ^b All %de were determined against authentic diastereomeric mixtures by GC or NMR.



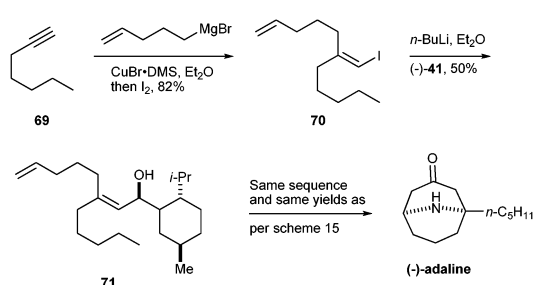
Scheme 15 Steric protection of the internal alkene: synthesis of (+)-euphococcinine.

(*vide infra*). Wittig rearrangement product **63** was obtained from **62** with complete stereoselectivity at the quaternary carbon and as a mixture of alcohol stereoisomers.

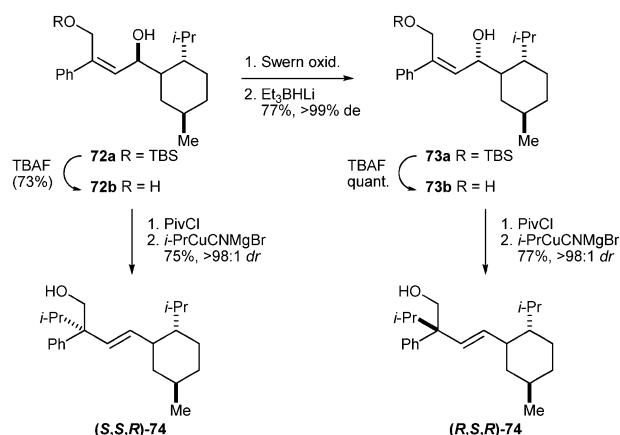
Yet another uncovered advantage of the menthyl chiral auxiliary is its capacity to sterically (kinetically) protect the internal double bond of the product, allowing one to perform chemistry on a distal double bond without prematurely cleaving the chiral auxiliary. For example, the oxidative cleavage of the terminal double bond in **64** was possible, provided that no excess periodate was used (Scheme 15). A ring-closing metathesis to give an eight-membered ring (**67**) occurred when **66** was treated with Grubb's 2nd generation catalyst. The formation of the six-membered ring product should have been preferred but it was prevented by the steric congestion provided by the auxiliary around the internal alkene. We used **67** to achieve a short and efficient synthesis of the coccinellid alkaloid (+)-euphococcinine (Scheme 15).⁴²

(-)-Adaline is another coccinellid alkaloid from the defensive secretion of lady bug *Adalia bipunctata* but it has the opposite absolute configuration at the quaternary carbon center.⁴³ The easy solution to its synthesis should have been to start with the enantiomer of the auxiliary, *i.e.* (+)-**41**. However, (-)-adaline can be, and was, synthesized starting from (-)-**41** simply by choosing the proper geometry of the starting alkene. Carbocupration of **69** gave **Z-70** (Scheme 16). Metal-halogen exchange and addition to (-)-**41** proceeded to give **71**. All other reactions and yields for the synthesis of (-)-adaline were nearly identical to the ones shown in Scheme 15 for (+)-euphococcinine.⁴²

Should the required geometry of the trisubstituted alkene be unavailable, one can still attain either enantiomer of the end



Scheme 16 Synthesis of (-)-adaline.



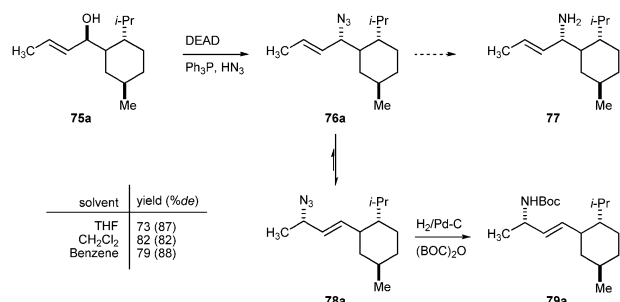
Scheme 17 Divergent syntheses of (*S,S,R*)-**74** and (*R,S,R*)-**74**.

product by changing the configuration of the allylic carbinol. For example, alcohol **72b** led to both diastereomers (*S,S,R*)-**74** and (*R,S,R*)-**74**, having opposite stereochemistry at the chiral quaternary carbon, *via* the divergent routes shown in Scheme 17. Divergent syntheses can be much shorter and more efficient than parallel syntheses because one is able to make both stereochemically pure enantiomers from a common intermediate, thus avoiding the repetition of many chemical steps.

The highly diastereoselective reduction by Et_3BHLi shown in Scheme 17 proved in fact general for all ketones of this type that we have tried but, surprisingly, only this hydride reagent provides such a level of selectivity. The Felkin-Ahn model of addition explains the stereochemical result but the high level of selectivity achieved is harder to explain given that other hydrides (NaBH_4 , RedAl , DIBAL-H , *etc.*) give very low levels of stereoselectivity (ratios of the same diastereomers vary from 1 : 1 to 2 : 1 in these cases).

Introducing a heteroatom

Now that we were equipped to make 3° or 4° stereogenic carbons with exquisite enantiomeric purities, we set about introducing heteroatoms at the newly formed stereocenter. Nitrogen seemed particularly interesting seeing as amino acids or alkaloids could be prepared this way. There are a number of ways one can transfer a heteroatom by allylic rearrangements from allylic alcohols like **75** (Scheme 18). However, our first attempts to do it *via* the classic Overman rearrangement⁴⁴ failed, mostly due to decomposition. Variations on this

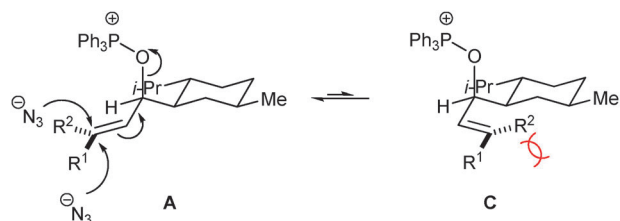


Scheme 18 Mitsunobu reaction of **75a** and sigmatropic rearrangement of allylic azides **76a** and **78a**.

rearrangement also failed for the same reason. In fact, rearrangements requiring heat or metal-catalysis were all inefficient.⁴⁵ We ascribed this problem to the somewhat sensitive nature of the allylic intermediates involved, prone to create an allylic carbocation instead of rearranging, especially if aromatic substituents are present on the double bond.

Unimpressed with the results of these first attempts, we turned our attention to introducing an oxygen atom instead. We thus attempted to create amine **77** (Scheme 18) with the intent of subsequently alkylating and oxidizing it and performing a Meisenheimer rearrangement⁴⁶ on the resulting *N*-oxide, thus achieving a transfer of oxygen from one allylic position to the next. The Mitsunobu displacement of an alcohol **75a** by sodium azide seemed as good a means as any to make **77**. We were a bit surprised to find only azide **78a** had formed.⁴⁷ Reduction/protection gave carbamate **79a** as the sole product in good yield and with a decent diastereomeric excess (Table in Scheme 18). Allylic azides are known to undergo a reversible and fast 3,3-sigmatropic rearrangement at room temperature.⁴⁸ This case is no exception, but several features are worth noting. First, because the diastereoselectivity is so high, we suspected that a direct S_N2 displacement, as envisaged, occurs principally, followed by an equilibration of the two allylic azides **76a** and **78a**. The rearrangement itself is concerted and does not cause any loss in diastereomeric purity.⁴⁹ Given that the allylic alcohol **75a** was diastereomerically pure before the Mitsunobu reaction, it follows that the small decrease in diastereomeric purity observed in **79a** must come from a partial S_N2' displacement of the phosphine oxide on conformation **A** by the azide ion, which occurs unselectively (Scheme 19). Neither the solvent polarity nor the size of the phosphine used had much effect on the yield or diastereoselectivity of the reaction.⁵⁰

On the other hand, substituents R¹ and R² had a substantial effect on the diastereoselectivity of the reaction (Table 2).⁵⁰ Large groups (R¹) reduced the amount of S_N2' attack and led to a slight increase in diastereoselectivity (Table 2, compare entries 2 vs. 1 and 3 vs. 4). Aromatic groups directly attached to the double bond (R¹) augmented the amount of S_N2' attack, which was accompanied by a decrease in diastereoselectivity (entries 6 and 7). We believe this is due to an increase in the partial positive charge on that carbon. In addition, conjugation pushed the equilibrium between **76g** and **78g** or **76h** and **78h** towards the conjugated products **76g,h**. A trisubstituted double bond in **75j** produced an azide product **79j** with a lower diastereoselectivity (entry 9). Again, an extra substituent brings a larger positive character at that alkene carbon and



Scheme 19 Origin of the small loss in diastereoselectivity in the displacement of the phosphine oxide by the azide ion.

Table 2 Effect of alkene substitution on the diastereoselectivity of the Mitsunobu reaction and on the equilibrium of the final azides

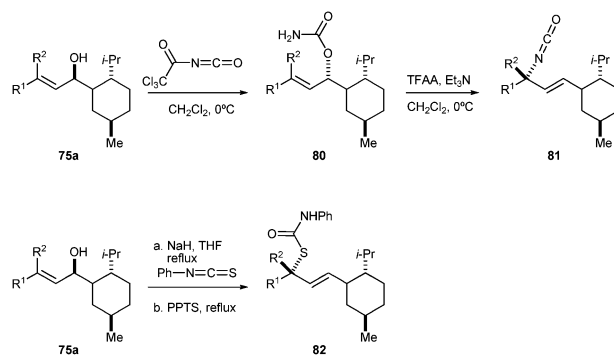
Entry	R ¹	R ²	76,78	76 : 78	Yield ^a (%)	%de ^b
1	CH ₂ OTBS	H	b	2 : >98	76	>96
2	CH ₂ Ph	H	c	2 : >98	80	94
3	<i>n</i> -Bu	H	d	2 : >98	80	82
4	<i>t</i> -Bu	H	e	2 : >98	78	88
5		H	F	2 : >98	81	94
6	Ph	H	G	94 : 6	78	33
7		H	H	98 : 2	98	60
8	SiMe ₃	H	I	1 : 1	81	>96 ^c
9	<i>n</i> -C ₅ H ₁₁	Me	J	2 : >98	70	60

^a Isolated yields. ^b %de of the major compound. ^c %de of each **76** and **78**.

favors more S_N2' attack resulting in a lower stereoselectivity. A trimethylsilyl group is so large that a 1 : 1 equilibrium mixture of the two regioisomers **76i** and **78i** ensues (entry 8). However, both **76i** and **78i** are diastereomerically pure. In this case, the S_N2' attack is disfavored for steric and electronic reasons and both regioisomers **76i** and **78i** must originate from **76i**.

This methodology was ideal to make unnatural amino acids quickly and efficiently.⁵⁰ One caveat, though, is that any loss of diastereoselectivity ultimately translates into a lower enantiomeric purity because the diastereomeric azides **78** are usually inseparable as are any subsequent diastereomeric amine derivatives. This is not surprising given that the double bond in **78** effectively isolates the chiral centers from one another. Indeed, even their NMR spectra are nearly identical.

To circumvent this problem, we used the rearrangement of cyanate to isocyanate (Scheme 20, top).⁵¹ This methodology has not been utilised a great deal in natural products synthesis,



Scheme 20 Sigmatropic rearrangements of cyanates and thiocarbamates.

Table 3 Yields and stereoselectivities of the rearrangement of cyanates derived from **80**

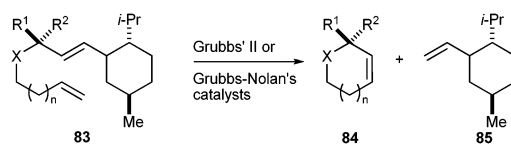
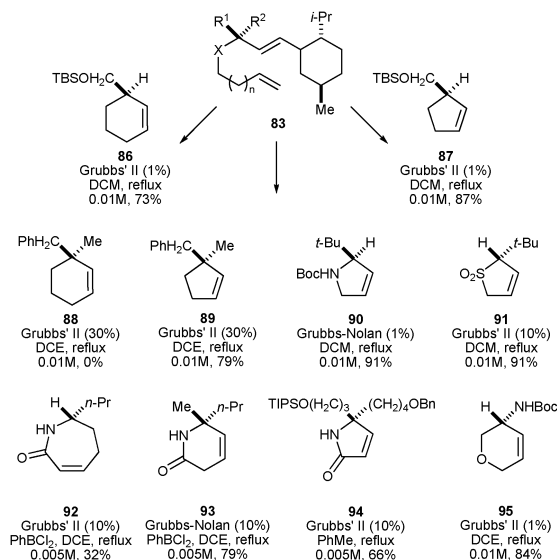
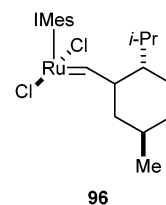
Entry	R ¹	R ²	Yield of 81 ^a (%)	%de of 81 ^b
1	<i>n</i> -Pr	H	96	> 99 : 1
2	<i>t</i> -Bu	H	93	> 99 : 1
3	SiMe ₃	H	93	98 : 2
4	<i>n</i> -Pr	Me	99	> 99 : 1
5	Ph	Me	80	97 : 3
6	Bn	Me	99	> 99 : 1

^a Isolated yields. ^b Determined by GC, HPLC, or NMR.

though Isobe, Ichikawa and coworkers have made lovely contributions using this rearrangement.⁵² It is a slight detour compared to the Mitsunobu strategy in that it takes two distinct steps to convert the alcohol to a cyanate but the rearrangement is instantaneous at room temperature and the transfer of chirality is impeccable. Importantly, it is irreversible, which allows aromatic substituents to be present on the allylic moiety (Table 3, entry 5).⁵³ Moreover, the rearrangement is diastereospecific and because there are no issues with two sites of attack, as was the case in the Mitsunobu strategy, the %de of the rearranged products is very high indeed (entries 1–6). A sulfur atom is also easily introduced from the rearrangement of a *O*-thiocarbamate (Scheme 20, bottom).⁵⁴

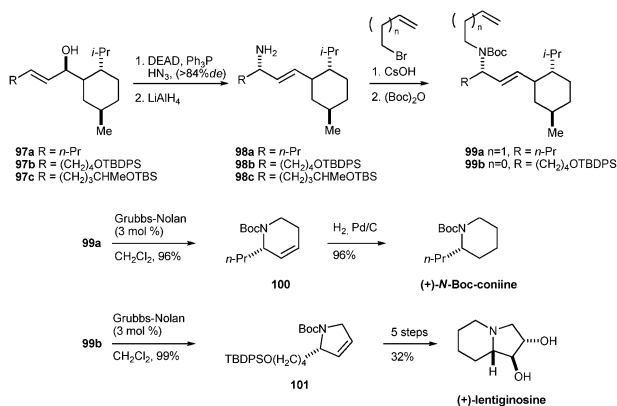
We were seriously contemplating the total synthesis of alkaloids at this stage for two reasons: (a) we were armed with three ways of obtaining a chiral carbon bearing nitrogen (Curtius, Mitsunobu displacement, and cyanate rearrangement); (b) we had just finished a study of the feasibility of cleaving the auxiliary using a ring-closing metathesis (RCM) reaction (Scheme 21).⁵⁵ This later synthetic possibility excited us very much for several reasons. Firstly, the extra step normally required to cleave a chiral auxiliary is forgone in as much as a RCM step was included in the synthetic design. Secondly, the derivative **85** is very volatile (bp < 100 °C) and removing it from the mixture is as simple as removing solvent. Thirdly, recovering **85** is also simple and converting it back to the original auxiliary **41** can be performed in high yield by ozonolysis. When R¹ or R² in **83** is a hydrogen, X can be anyone of carbon, oxygen, nitrogen, or sulfur and excellent yields of five and six-membered rings (**84**, *n* = 0 or 1) carbo- or heterocycles can be obtained.⁵⁶

Scheme 22 shows typical examples and a few interesting notes are in order at this point.^{50,56} Five-membered rings (**86**) form much faster and in higher yields than the homologous six-membered rings (**87**). In fact, all-carbon quaternary chiral centers (**83**, X, R¹, R² = C, Scheme 22) prevent the formation of six-membered rings all-together (**88**) while five-membered rings are formed, albeit using a high catalyst loading (**89**). From those observations, we deduce that the ring formation is irreversible under those conditions. α,β -Unsaturated amides are surprisingly good substrates (**92–94**), given that electron-poor alkenes are usually unreactive towards the ruthenium catalyst to initiate the RCM reaction.⁵⁷ We believe that the success of many of the RCM reactions shown in Scheme 22 is partly due to the stability of the propagating ruthenium catalyst **96** (Fig. 4), which will be more stable to long reactions

**Scheme 21** Cleavage of the chiral auxiliary by RCM.**Scheme 22** Carbo- and heterocyclic compounds prepared by RCM cleavage of the chiral auxiliary.**Fig. 4** Propagating catalyst species unique to our system.

time and high temperatures. This increased stability will keep the catalyst active longer, eliminate the need for higher catalyst loading and curb side reactions caused by species emanating from the catalyst's decomposition.⁵⁸ In addition, the bulky menthyl fragment in **96** may slow re-coordination with a phosphine ligand, thereby keeping the catalytic species active.

The generation of an endocyclic double bond in the RCM product is a key feature of our general strategy. It represents a powerful synthetic lever on which to perform a host of other transformations, including forming polycyclic structures. With that in mind, we undertook the total syntheses of natural polycyclic alkaloids, starting with structures of lower complexities, such as conicine⁵⁹ and lentiginosine⁶⁰ (Scheme 23), where the transformation involving the double bond is simple. To that end, the alcohols **97a–c** were prepared in a single step from the corresponding vinyl iodides. Mitsunobu reactions and reductions gave amines **98a–c** and then **98a** and **98b** were mono-alkylated⁶¹ with butenyl or allyl bromide, respectively, to give **99a** and **99b**. Their RCM reactions proceeded to give the six- or five-membered *N*-heterocycles **100** or **101**, respectively, in excellent yields. The synthesis of

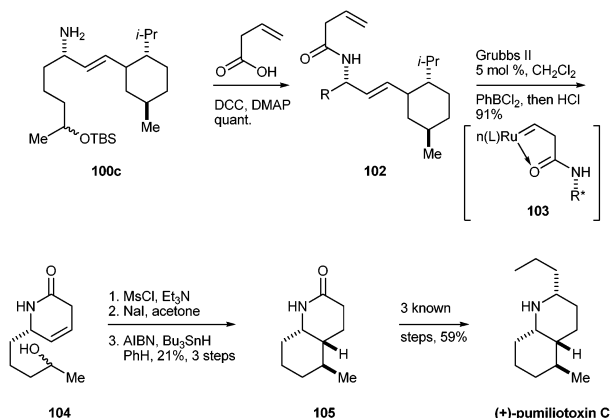


Scheme 23 Synthesis of (+)-lentiginosine.

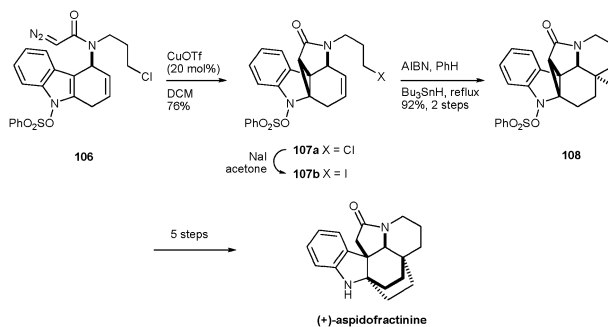
coniine required the simplest transformation possible for an alkene, *i.e.* its hydrogenation, but lentiginosine was accessed by using the alkene to introduce C–O bonds by stereoselective epoxidation. Epoxidation of **101** took place from the least hindered face and later water opened the epoxide at the least hindered position. Three more steps of deprotection and cyclisation completed the synthesis.⁵⁰

We were particularly interested in using the endocyclic double bond, to form a carbon–carbon bond and extra rings. To that effect, compound **98c** (*cf.* Scheme 23) was first acylated with butenoic acid and an RCM reaction in the presence of an external Lewis acid was carried out to give **104** in 91% yield (Scheme 24).⁵⁰ The external Lewis acid was necessary to prevent the detrimental formation of a five-membered ring chelate between the amide oxygen and the ruthenium (**103**) once initiation has taken place. As a bonus, the protecting silyl group was cleaved during work-up, presumably because of the fortuitous formation of HCl. We added extra HCl after the reaction, to ensure complete deprotection.

Conversion of the alcohol in **104** to a radical precursor and its treatment with the usual tin-based radical reaction conditions gave **105** in poor yield but excellent stereoselectivity. The synthesis of pumiliotoxin C was completed using three known steps.⁶² The low-yielding radical cyclization step was counterbalanced by several quantitative yields along the synthesis, such that the overall efficiency of this synthesis was high (15 steps, 6% overall yield, average of 81% per step).⁵⁰



Scheme 24 Synthesis of (+)-pumiliotoxin C.

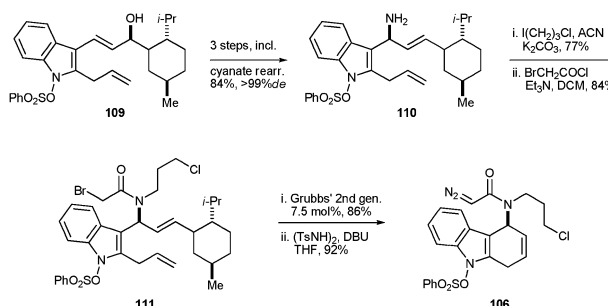


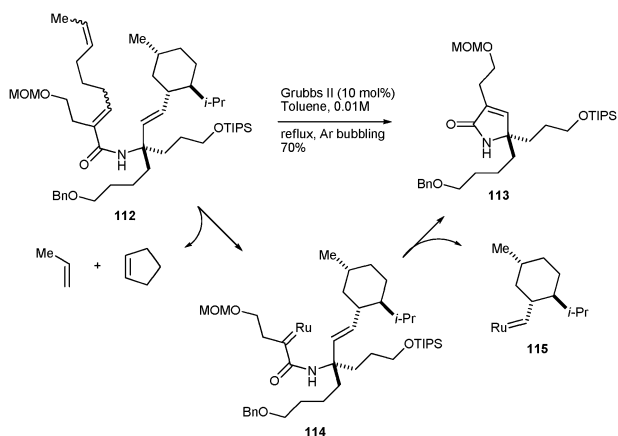
Scheme 25 Total synthesis of (+)-aspidofractinine.

Radical cyclization to form decalines or perhydroquinoline-type structures, such as **105**, are actually known to be difficult.⁶³ Yet, we performed a very similar radical cyclisation on structure **107b**, during our synthesis of aspidofractinine, with far more success (Scheme 25).⁶⁴ Iodide **107b** underwent essentially the same cyclization as per the iodide derived from **104** but in 92% yield with no apparent products emanating from hydrogen abstraction events. It is tempting to thank the rigidity of the structure brought about by the presence of a cyclopropane for the high yield of **108** and, indeed, we believe that it both increases the rate of cyclization and decreases the stability of a potential radical centered on the carbon bearing the amide nitrogen (its delocalisation on the π system of the double bond becomes disfavored because of angle strain). The synthesis of (+)-aspidofractinine (+12, $c = 0.27$, CHCl₃) was completed in five subsequent chemical steps (Scheme 25), including the concomitant deprotection of the indole nitrogen and opening of the cyclopropane in **108**. The natural product had been assigned the stereochemistry shown in Scheme 25 but with a negative optical rotation (-14 , $c = 0.28$, CHCl₃), which compelled us to propose that it actually has the opposite absolute stereochemistry than that shown in Scheme 25.

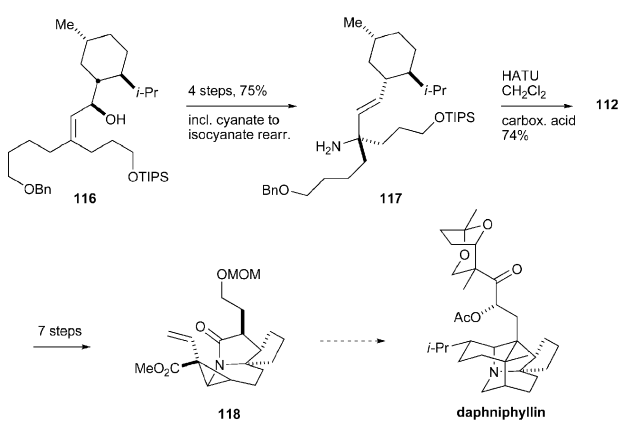
Of course, diazo **106** had been prepared according to our strategy as shown in Scheme 26. The cyanate to isocyanate rearrangement worked as planned with complete transfer of the chirality from the alcohol **109** to the amine **110**, after deprotection of the intermediate carbamate. Alkylation and acylation of **110** led to compound **111**, which underwent a facile RCM reaction to give a cyclic intermediate and eventually **106**, both very prone to aromatization.

Finally, we have engaged the total synthesis of the complex alkaloid daphniphyllin (*cf.* Scheme 28).⁶⁵ The yield obtained in the relay RCM reaction of compound **112** is impressive given

Scheme 26 Synthesis of diazo compound **106**.



Scheme 27 An impressive relay RCM reaction.



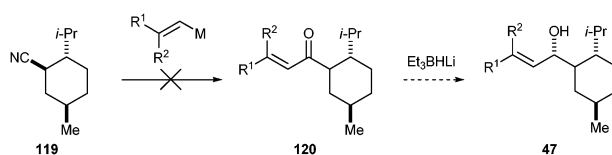
Scheme 28 Towards the synthesis of daphniphyllin.

the steric crowding around the disubstituted double bond (Scheme 27). It also underscores the power of the relay RCM strategy.⁶⁶ We firmly believe that the chiral auxiliary, again, plays an essential role in stabilising the ruthenium complex **115** so that higher temperatures and longer reaction times can be used to good effect.⁵⁸ The seemingly superfluous methyl at the end of the relay chain in **112** is actually important as it prevents intermediate **114** from biting back that double bond, a process that effectively competes with the desired cyclisation in the case where that alkene is terminal.

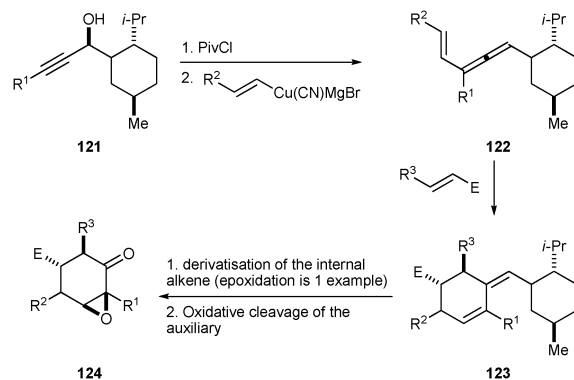
The precursor **112** was obtained in 5 steps from the 'usual' chiral alcohol **116** in good overall yield. The latter has been transformed to the advanced intermediate **118** but low yields in that latter sequence have hampered our efforts at completing the synthesis so far. The main culprit is a cyclopropanation reaction, which yields only 16% of the desired product cyclopropane in **118**. Improvement of this route and further studies to complete the synthesis are currently underway.

Future directions

We would like to develop yet a third generation chiral auxiliary, one with all the advantages of *p*-menthane-3-carboxaldehyde **41** that we described herein but with the added benefit of being more air stable. Indeed, a slow air oxidation of *p*-menthane-3-carboxaldehyde into the



Scheme 29 *p*-menthane-3-carboxynitrile **119** and its potential use as a stable 3rd generation chiral auxiliary.



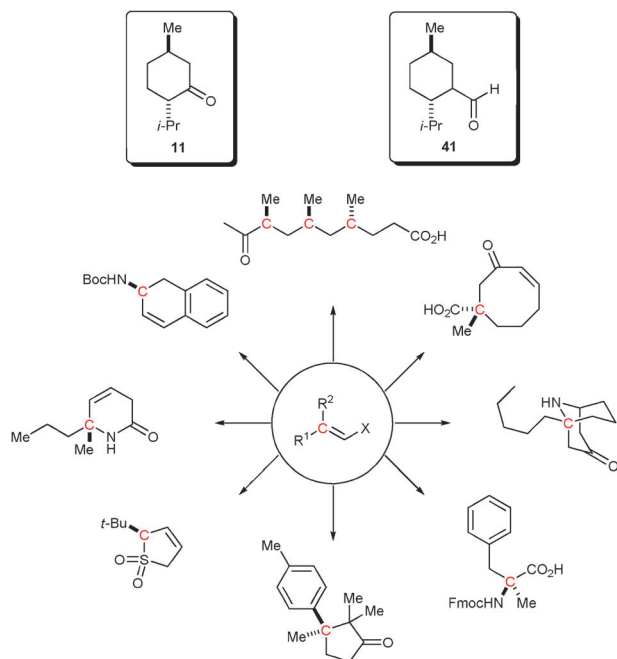
Scheme 30 A sequence of reactions to prepare chiral non-racemic cyclohexanone derivatives.

corresponding carboxylic acid impedes on its potential commercialization. We have prepared the air-stable, crystalline *p*-menthane-3-carboxynitrile **119** (Scheme 29) but we have been unable, so far, to add vinylmetals to it in decent yields. As stated earlier, the stereoselective reduction of the resulting ketone **120** is possible with superhydride™. Efforts are continuing towards this goal.

Chiral vinylallenes like **122** could be easily prepared from the corresponding alkyne **121** by a stereospecific cuprate addition (Scheme 30). We and others have shown several years ago that dienophiles will add stereoselectively to such vinylallenes giving a single geometry of the exocyclic double bond.⁶⁷ The regioselectivity shown is the one expected from steric and electronic arguments, but the stereoselectivity will vary depending on the dienophile. Figuring out a way to differentiate the two double bonds in **123** should be possible since we have already demonstrated that it is possible to perform chemistry on other alkenes in the presence of the one next to the auxiliary (*cf* Scheme 15). For example, it should be possible to epoxidize the internal alkene. If so, we could use this strategy to prepare highly substituted chiral non-racemic cyclohexanone derivatives, complementing what exists in the literature.⁶⁸ We suspect that if successful, the method would benefit from a high substrate scope, which has been the trademark of this chiral auxiliary in all of the reaction sequences developed so far.⁶⁹

Conclusions

Alternatives to chiral enolate chemistry are more numerous than may appear and they constitute important tools for synthetic chemists.⁷⁰ One strategy described in this account uses menthone in conjunction with the S_N2' displacement reaction by cuprate reagents to offer, in a complementary way, an alternative to the alkylation of chiral enolates.



Scheme 31 Transformations of simple vinylic starting materials into products having a 3° or 4° chiral carbon.

The level of stereoselectivities achieved compares favourably with that of the best chiral enolates published, as does its scope.

Although *p*-menthyl-3-carboxaldehyde **41** may not have been the obvious first choice as a chiral aldehyde for developing the wide array of transformations shown in Scheme 31, that chiral auxiliary has proven irreplaceable in many instances and helped in increasing reactivity and selectivity in many of the transformations we have studied. It is our hope that more research groups will opt to use this strategy as a useful method to build their desired chiral carbonyl compounds.

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