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p-Menthane-3-carboxaldehyde: A Useful Chiral Auxiliary for the Synthesis of Chiral Quaternary Carbons of High Enantiomeric Purity

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Abstract: (+)- or (−)-*p*-Menthane-3-carboxaldehyde is made in two easy steps from (+)- or (−)-menthone, respectively. This auxiliary allows for the synthesis of carbonyl compounds bearing a α-chiral quaternary carbon. The flexibility, efficiency, and ease of use of the method are demonstrated in a series of examples, which include the total synthesis of (+)-cuparenone as well as a partial synthesis of (−)-cassiol.

Introduction

Compounds bearing a chiral quaternary carbon center are ubiquitous in nature. Their construction poses a difficult challenge to the synthetic chemists, especially those centers bearing only carbons.[1] The difficulty resides principally in achieving stereoselection on a precursor that bears similar appendages on its pro-chiral carbon. For example, the preparation of α-monosubstituted chiral enolates of defined geometry is easily achieved nowadays and allows for the preparation of carbonyl compounds bearing a α-chiral tertiary center.[2] However, the analogous α,α-disubstituted chiral enolates are much harder to make and their stereoselective alkylation is not straightforward.[3] Stereospecific reactions offer an attractive solution to this problem. This is the case of the copper-mediated S_N2' substitution of chiral allylic esters of defined geometries followed by oxidative cleavage of the resulting alkene (Figure 1). Recently, several systems based on the S_N2' displacement of an allylic leaving group were developed to make nonracemic tertiary carbon centers,[4] but only a few were designed to create chiral quaternary carbons.[5] The allylic alcohol precursors are relatively easy to prepare in high stereochemical purity by the stereoselective reduction of enones or the stereoselective additions of vinylmetals to aldehydes or ketones. In principle, the chirality of these allylic alcohols can then be transposed to the distal vinylic position by several types of rearrangements or displacement reactions (vide infra).

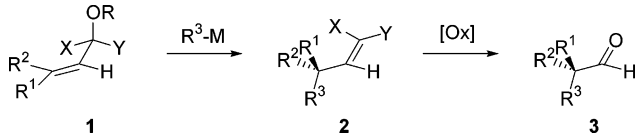

Figure 1. The S_N2' displacement as a stereospecific reaction for the creation of a quaternary chiral center.

Although this basic concept has been around for a while,[6] the development of systems of wider scope and applicability is only recent.[4,5] Kakinuma and co-workers were the first to describe a functional system based on a sugar-derived furanone that allowed the synthesis of carbonyl compounds bearing an α-chiral tertiary carbon (Scheme 1).[6a,b] Only rearrangement reactions of the allylic alcohol were reported with their system. S_N2' displacement reactions were not reported for this system presumably because metal π-complex formation would be hampered by $A^{1,3}$-strain. In 1998, we described a system based on menthone (**7**) as a chiral auxiliary that allowed S_N2' displacement reactions to take place with great efficiency (Scheme 2).[4a,b] Conformer **8A** was more than 4 kcal/mol more stable than the other reactive conformer **8C** (Figure 2). However, rearrangement reactions were not possible on this system because of the hindered nature of the tertiary alcohol, which proved exceedingly resilient to derivatization. Moreover, neither menthone (**7**) nor Kakinuma's furanone **4** could be used to prepare quaternary carbon centers because the substituent R^2 increases

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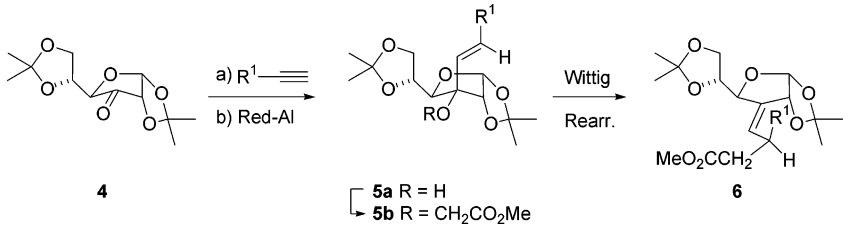
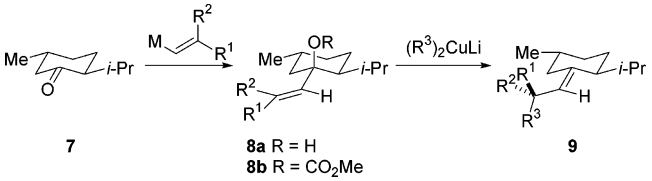
10.1021/ja046084j CCC: $27.50

Scheme 1. Kakinuma's Furanone Chiral Auxiliary System



Scheme 2. Menthone Chiral Auxiliary System



the steric congestion and raises considerably the energies of conformations **A** or **C** because of increased $A^{1,3}$ strain (Figure 2, $R^2 \neq H$). In fact, even compound **8b** where $R^1 = H$ and $R^2 = Me$ would not undergo a displacement reaction. Clearly, an aldehyde as chiral auxiliary would be a better choice when dealing with trisubstituted alkenes ($R^2 \neq H$), because it would lead to allylic alcohol derivatives **1** with substantially lower $A^{1,3}$ strain in one reactive conformer (cf. Figure 1, X = H).

We have recently described a methodology based on p-menthane-3-carboxaldehyde **10** that allows the formation of quaternary carbon centers of high stereochemical purity (Scheme 3).[5a] Aldehyde **10** is made in two easy steps from menthone. S_N2' displacement reactions of the pivalate esters derived from the alcohols **12** and **13** successfully transfer chirality to the distal alkene carbon giving quaternary or tertiary chiral carbons of high stereochemical purity. Herein, we report that rearrangement reactions are also successfully used for the formation of quaternary carbon centers of high enantiomeric purity, including the synthesis of α,α-dialkylated amino acids, a synthesis of natural product (+)-α-cuparenone, and a partial synthesis of the unnatural enantiomer of antiulcerogenic (+)-cassiol.

At the heart of this strategy lies the stereoselective addition of vinylmetals **11** to an α-chiral aldehyde (Scheme 3). From the onset, only bulky aldehydes were considered as viable chiral auxiliaries because we believed that bulk would favor an S_N2' regioselectivity in the ensuing displacement reaction.[4c,7] While *p*-menthane-3-carboxaldehyde **10** certainly fits this criteria, the chances of adding to it a vinylmetal **11** in a highly stereoselective fashion were deemed small (cf. Scheme 3). The chiral center α to the aldehyde in **10** is flanked by two similar alkyl groups that would seem to preclude high stereoselectivity in nucleophilic additions as predicted by the Felkin−Anh model.[8] This appeared to be indeed the case, as vinyllithium or vinylmagnesium reagents **11** (M = Li or MgX) failed to deliver the two alcohols **12** and **13** in ratios exceeding 2:1. We would have immediately shyed away from **10** were it not for the serendipitous discovery that vinylalanes **11** ($M = AlMe_2$), generated by the zirconium-catalyzed carboalumination of alkynes, reacted with high stereoselectivity with **10** to give the alcohol **12** as the major diastereomer. We derivatized **12a** and **13a** into the corresponding Mosher esters[9] which allowed us to determined that the major alcohol **12a** originated from a "Felkin−Anh" addition of the vinylalane on **10**.[5a] We made a series of allylic alcohols **12** using this method (Table 1, method A). Reports of the addition of vinylalanes to aldehydes are scant[10] and we were first to report their stereoselective addition to chiral aldehydes.[11] The reason for this enhanced stereoselectivity eluded us for some time until we realized that the excess trimethylaluminum used to generate the vinylalane, as per the Negishi protocol,[12] was in fact responsible for the high stereoselectivity.[13] To our surprise and delight, vinyllithiums **11** (M = Li) added with even greater selectivity than vinylalanes to aldehyde **10** in the presence of various amounts of trimethylaluminum.[13] Other α-chiral aldehydes also gave increased Felkin−Anh selectivities upon addition of $AlMe_3$ to the vinyllithium solution prior to addition to the aldehyde.[13] This observation is interesting in its own right and is the subject of ongoing mechanistic studies in our laboratory. Crude allylic alcohols **12** were obtained as 30 to 80:1 mixtures of diastereomers (Table 1, method B). The nature of the vinyl substituent seems to bear little effect on the outcome making this a general way to make a wide variety of di- and trisubstituted allylic alcohols from **10**. Moreover, in all cases studied thus far, the diastereomeric alcohols **12** and **13** were easily separated by normal silica gel column chromatography, making this an efficient method to procure diastereomerically pure alcohols **12**. The yields given in Table 1 represent the yield of isolated diastereomerically pure **12**.

While attempting to develop a system suitable for amino acid synthesis (vide infra), we discovered a highly stereoselective and efficient way to prepare diastereomerically pure allylic

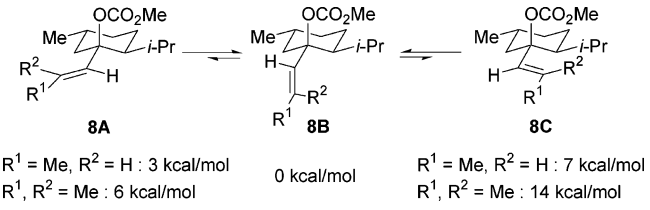


Figure 2. Different conformations of allylic alcohols **8**.

(7) Regioselectivity is dependent on the nature of the cuprate reagent but also on the allylic substrate. See Tseng, C. C.; Paisly, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884−2891 as well as ref 15.
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(12) Negishi, E.-I.; Kondalov, D. Y. *Chem. Soc. Rev.* **1996**, 417−426 and references therein.
(13) Spino, C.; Granger, M.-C.; Tremblay, M.-C. *Org. Lett.* **2002**, *4*, 4735−4737.

Scheme 3. Stereoselective Addition of Vinylmetals to Menthyl 3-Carboxaldehyde **10**

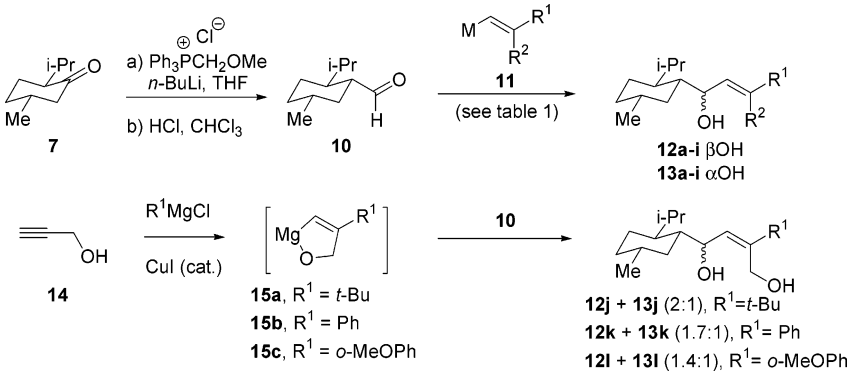

Table 1. Comparison of Ratios of Alcohols **12**:**13** Obtained by Two Different Methods Involving $AlMe_3$

entry	11	R^1 (R^2 = Me)	12/13	12:13 ratio[a] (% yield)[b] method A[c]	method B[d]
1	**11a**	*n*-Bu	**a**	12:1 (70)	
2	**11b**	*n*-Pen	**b**	9:1 (75)	80:1 (60)
3	**11c**	*c*-C_6H_{11}	**c**	14:1 (80)	
5	**11d**	Bn	**d**	11:1 (76)	
6	**11e**	CH_2OH	**e**	10:1 (quant)	
7	**11f**	$(CH_2)_3OTBS$	**f**	10:1 (71)	
8	**11g**	$(CH_2)_4OTBS$	**g**	11:1 (68)	
9	**11h**	Ph	**h**	18:1 (63)	34:1 (50)
10	**11i**	*p*-tolyl	**i**	24:1 (78)	39:1 (76)

[a] All ratios measured by G. C. or NMR of the crude mixtures. [b] Isolated yield of pure **12**. [c] Method A: alkyne, Cp_2ZrCl_2 (cat.), $AlMe_3$, CH_2Cl_2, aldehyde **10**. [d] Method B: vinyllithium, $AlMe_3$, ether, aldehyde **10**.

alcohols **13**. It started with the carbomagnesiation of propargyl alcohol **14** giving cyclic trisubstituted vinylmagnesiums **15** (Scheme 3).[14] These organometallic species add efficiently to aldehyde **10** albeit with only slight selectivity favoring alcohol **12** over **13**. After selective protection of the primary alcohol in the mixtures of **12j**−**l** and **13j**−**l**, oxidation of the mixtures of allylic alcohols under the Swern conditions gave the corresponding ketone **16a**−**c** (Scheme 4, top). Unexpectedly, lithium triethylborohydride reduced each ketone **16** with complete facial selectivity to give only the corresponding alcohol **13m**−**o**. Alcohols **12a** and **12i** were also converted to **13a** and **13i**, respectively, using this protocol (Scheme 4, bottom). The stereochemistry of the alcohols **13** correspond to a Felkin−Anh addition of the hydride to the corresponding ketones, and thus this procedure establishes the opposite absolute configuration at the carbinol carbon when compared to the Felkin−Anh addition of a vinylmetal **11** to aldehyde **10** (cf. Scheme 3). In contrast, reduction of **16** using sodium borohydride or Dibal-H gave predominantly alcohol **12**, of opposite stereochemistry, with selectivities ranging from 2 to 4:1. The origin of the facial selectivity with Et_3BHLi is not yet understood but here too the selectivity seems to have little sensitivity to the alkene substituent as ketones **16** bearing aryl, alkyl, hydroxymethyl, or *tert*-butyl groups all gave a single diastereomer upon reduction with Et_3BHLi.

To enhance the attractiveness of this route, a more direct access to ketones **16** was developed. The reaction of acyl chloride **19**, available in three steps from menthone (**7**), with vinylsilane **18** gave enone **16f** having the *E* geometry (Scheme 5). Many Lewis acids catalyze this reaction but tin tetrachloride gave the highest yields of **16f** (70−75%). This ketone was reduced with Et_3BHLi to give **13p** as a single diastereomer. Admittedly, the yield of this coupling reaction was variable on larger scale (>10 g) and decomposition products sometimes accompanied the desired product, which leaves the oxidation/reduction sequence a more reliable method so far. We are presently developing alternatives to using acyl chloride **19**.

With firm methods to prepare allylic alcohols **12** or **13** diastereomerically pure, we set about studying various ways to transfer the chirality of the carbinol to the distal carbon of the olefin. The first transformation that we studied was the addition of alkylcuprate reagents to ester derivatives (cf. Figure 1).[15] The issue of regioselectivity (**22a** vs **24**) was first investigated (Table 2). To avoid confusing mixtures of regioisomers and diastereomers, we added methylcopper species to **20a**, the ester derived from **12a**. Regioselectivity was strongly dependent on the nature of the leaving group and of the cuprate reagent. An acetate ester (entry 1) with Gilman-type cuprates gave the lowest S_N2'/S_N2 ratios. A carbonate (entry 7) gave slightly better results (2:1) while a carbamate (entry 5) gave unsatisfactory yields of product, giving back mostly starting material. Changing the nature of the cuprate to monoalkylcyano cuprate or higher order cuprate also gave unsatisfactory yields of product (entries 2−5, and 8). Using a pivalate ester in conjunction with $RCu(CN)Li\cdot BF_3$ (entry 9) gave a better, yet still unsatisfactory ratio (3:1). Finally, the use of Goering's conditions,[7] consisting of the addition of monoalkylcyano magnesiocuprates on pivalate esters, gave exclusively the desired regioisomer resulting from an S_N2' attack of the cuprate reagent on **20a** (R═Piv, entry 10). All subsequent substrates studied thus far afforded similar results. *p*-Menthane-3-carboxaldehyde undoubtedly plays a role in favoring the S_N2' displacement since Goering had shown that several of their substrates gave considerable amounts of S_N2 displacement under those conditions.[7]

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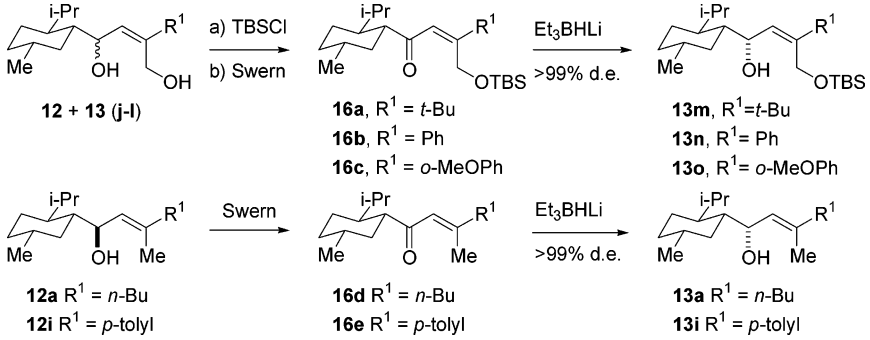
Scheme 4. Preparation of Alcohols **13a**,**i**,**m**−**o** by the Stereoselective Reduction of the Corresponding Ketone **16**



12 + **13** (**j**-**l**)

16a, R^1 = *t*-Bu
16b, R^1 = Ph
16c, R^1 = *o*-MeOPh

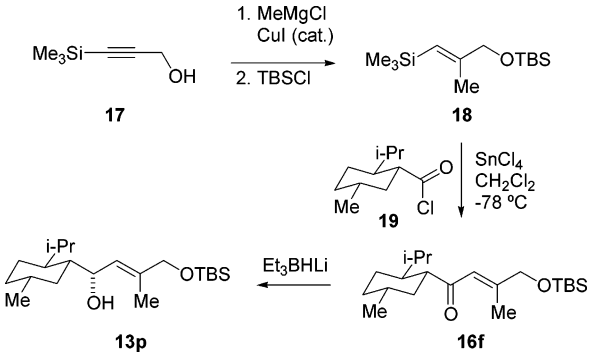
13m, R^1=*t*-Bu
13n, R^1= Ph
13o, R^1= *o*-MeOPh

12a R^1 = *n*-Bu
12i R^1 = *p*-tolyl

16d R^1 = *n*-Bu
16e R^1 = *p*-tolyl

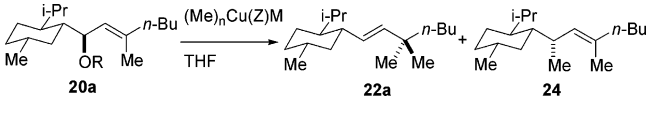
13a R^1 = *n*-Bu
13i R^1 = *p*-tolyl

Scheme 5. Synthesis of **13p** Using Acyl Chloride **19** as Chiral Auxiliary



17 **18** **19** **16f** **13p**

Table 2. S_N2'/S_N2 Ratios of Cuprate Addition on Allylic Esters **20**

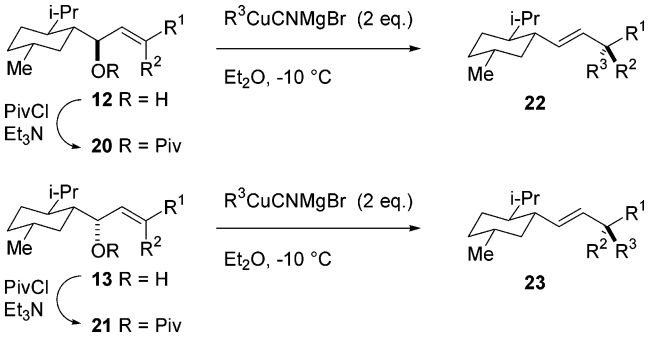


20a **22a** **24**

entry	R	cuprate	**22a:24** ratio[a]
1	Ac	Me_2CuLi	1:1.5
2	Ac	$Me_2Cu(CN)Li_2$	**12a**
3	Ac	MeCu(CN)MgBr	S. M.
4	CONHPh	MeCu	S. M.
5	CONHPh	Me_2CuLi	S. M.
6	CONHPh	MeCu(CN)MgBr	S. M.
7	CO_2Me	Me_2CuLi	2:1
8	CO_2Me	MeCu	1.5:1
9	CO-*t*-Bu	$MeCu(CN)Li{\cdot}BF_3$	3:1
10	CO-*t*-Bu	MeCu(CN)MgBr	>99:1

[a] Ratios measured by NMR of the crude mixtures.

Scheme 6. S_N2' Displacement of Pivalates **20** or **21** with Cuprate Reagents



22

23

Pivalates **20** and **21** were then subjected to these reaction conditions to give cuprate adducts **22** and **23**, respectively (Scheme 6). The results are compiled in Table 3. In all cases but one (entry 18), the transfer of chirality was essentially complete as judged by GC, HPLC, or NMR analysis of the crude mixtures. We made diastereomers **22** and **23** independently from pivalates **20** and **21**, respectively. This allowed us to unambiguously determine the ratio of **22** or **23** obtained in each separate reaction. As can be seen, the method is general. Primary or secondary alkylcuprates gave the desired adduct in good yields. However, larger cuprates such as *t*-BuCuCNMgBr or PhCuCNMgBr did not undergo the addition reaction (entry 4). This is hardly surprising, as the addition of a *tert*-butylcuprate would create two adjacent quaternary carbon centers. In phenylcuprate, the reason is less obvious and we suggest that it may be just a lack of reactivity of the cuprate reagent.

When a bulky substituent at the quaternary carbon center in **22** or **23** is needed, this substituent should preferably be part of the allylic alcohol (i.e., R^1 or R^2). For example, aryl groups as substituent R^1 on the pivalate allowed the synthesis of the desired adduct **22** or **23** using primary or secondary alkylcuprates (entries 18−20 and 22−23), demonstrating that interesting and sterically congested chiral quaternary carbons are accessible with this method. However, a *tert*-butyl group impeded the cuprate addition of ethyl or isopropyl cyanocuprates (entry 21).

Table 3. Yields and Ratios of Cuprate Addition on Allylic Pivalate Esters **20** or **21**

entry	piv.[a]	R^1	R^2	R^3	maj. prd.	**22:23**[b] (% yield)[c]
1	**20a**	*n*-Bu	Me	*i*-Pr	**22b**	>98:2 (90)
2	**20a**	*n*-Bu	Me	Et	**22c**	>98:2 (98)
3	**20a**	*n*-Bu	Me	*n*-Hep	**22d**	>98:2 (97)
4	**20a**	*n*-Bu	Me	*t*-Bu or Ph		(0)
5	**20c**	*c*-C_6H_{11}	Me	*i*-Pr	**22e**	>98:2 (95)
6	**20d**	CH_2Ph	Me	*i*-Pr	**22f**	>98:2 (92)
7	**20d**	CH_2Ph	Me	$H_2C{=}CH(CH_2)_2$	**22g**	>98:2 (88)
8	**20d**	CH_2Ph	Me	$H_2C{=}CH(CH_2)_3$	**22h**	>98:2 (91)
9	**21r**[d]	CH_2OH	Me	*i*-Pr	**23i**	>99:1 (98)
10	**21s**[e]	CH_2OSEM	Me	*i*-Pr	**23j**	>99:1 (57)
11	**21t**[e]	CH_2OBn	Me	*i*-Pr	**23k**	>99:1 (8)
12	**21p**	CH_2OTBS	Me	*i*-Pr		(0)
13	**20p**	CH_2OTBS	Me	$H_2C{=}CH(CH_2)_2$	**22l**	>99:1 (80)
14	**20f**	$(CH_2)_3OTBS$	Me	*i*-Pr	**22m**	>98:2 (95)
15	**20f**	$(CH_2)_3OTBS$	Me	Et	**22n**	>98:2 (89)
16	**20f**	$(CH_2)_3OTBS$	Me	$H_2C{=}CH(CH_2)_2$	**22o**	>98:2 (82)
17	**20g**	$(CH_2)_4OTBS$	Me	$H_2C{=}CH(CH_2)_2$	**22p**	>98:2 (41)
18	**20h**	Ph	Me	*i*-Pr	**22q**	91:1 (90)
19	**20n**	Ph	CH_2OH	*i*-Pr	**22r**	>99:1 (73)
20	**20o**	*m*-MeO-Ph	CH_2OH	Et	**22s**	>99:1 (86)
21	**21m**	*t*-Bu	CH_2OH	*i*-Pr or Et		(0)
22	**21n**	Ph	CH_2OH	*i*-Pr	**23r**	>1:99 (77)
23	**21o**	*m*-MeO-Ph	CH_2OH	Et	**23s**	>1:99 (64)

[a] For clarity, the pivalates bear the same letter as the alcohol they were formed from. [b] All ratios measured by G. C., HPLC, or NMR of the crude mixtures. [c] Isolated yields. [d] Obtained from the deprotection of **21p**. [e] Obtained from the protection of **21r**.

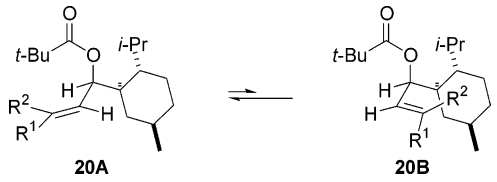


Figure 3. Conformational biases of pivalates **20**.

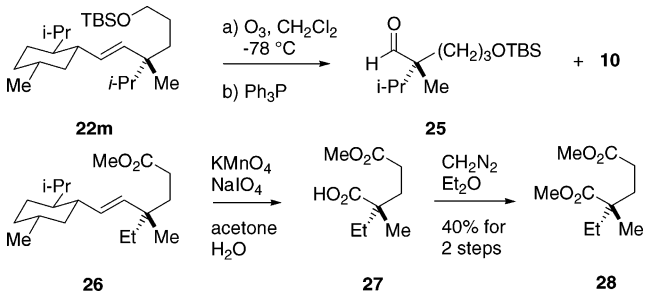
A hydroxymethyl (R^2) substituent gave high-yielding addition reactions (entries 9 and 19−23). Protecting this group slows the reaction considerably (or completely with a TBS group) when the cuprate reagent bears a bulky *i*-propyl group (entries 10−12). However, if the cuprate bears a primary alkyl, the yield of reaction is good (entry 13).

Either stereochemistry at the carbinol (i.e., **20** and **21**) gives, as expected, the same level of chirality transfer, but the adducts have the opposite absolute configuration at the quaternary carbon (entries 19 vs 22 and 20 vs 23). In fact, many cuprate addition reactions listed in Table 3 were carried out with both **20** and **21,** and in each case the same level of chirality transfer was observed. Although two diastereomers (**20** and **21**) can, in principle, have different reactivities, we believe that the controlling elements in the transfer of chirality are the anti-stereospecificity of the cuprate addition on allylic systems[16] and the conformational bias of the allylic ester toward conformations **20A** provided by $A^{1,3}$-strain (Figure 3). In support of this, adducts **22** with a *Z* double bond, resulting from addition to conformers **20B**, have never been observed (the same is true for adducts **23**). Ultimately, the menthyl nucleus serves to induce asymmetry at the carbinol carbon in **12** or **13** but it remains a spectator fragment in the following steps, as far as stereocontrol is concerned. However, it does play an important role in ensuring good regioselectivity in the cuprate displacement reaction on pivalates **20** or **21**.

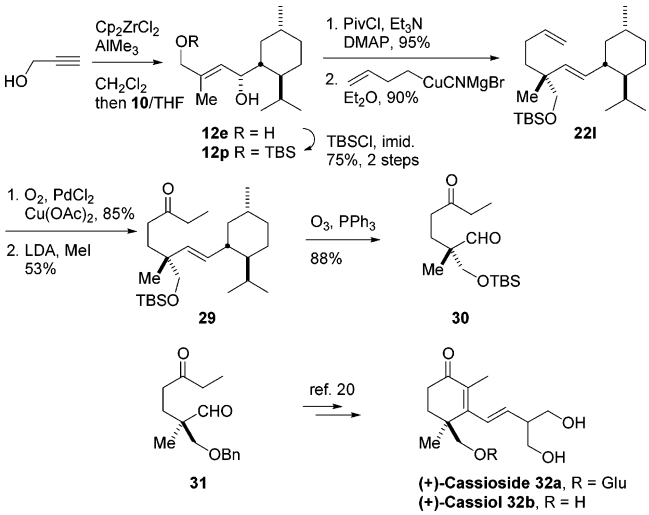
The lower stereoselectivity obtained in **20h** (entry 18) can be explained in terms of a mechanism involving ionic or radical intermediates. We had observed this phenomenon on another system based on menthone.[4a] When R^1 or R^2 in **20** or **21** is a group capable of stabilizing ions or radicals, such pathways may become competitive and lead to a less selective addition, especially when less reactive cuprate reagents are involved.

After the cuprate addition produces the chiral quaternary center, the chiral auxiliary is then oxidatively cleaved. Carboxylic acids, aldehydes, or primary alcohols can be easily accessed by ozonolysis followed by the appropriate workup. For example, aldehyde **25** was obtained in 65% yield along with *p*-menthane-3-carboxaldehyde **10** (80%) (Scheme 7, top). A mixture of potassium permanganate and sodium periodate was

Scheme 7. Oxidative Cleavage of the Auxiliary and Synthesis of the Known Compound **28**



Scheme 8. Synthesis of an Analog of Taber's Intermediate **31**



also able to cleave the auxiliary in **26** and release the desired carboxylic acid **27** (Scheme 7, bottom). The latter was transformed to diester **28**, a known compound for which the absolute stereochemistry has been determined,[17] allowing us to confirm our hypotheses about the stereochemical outcome of each key step in the sequence (i.e., Felkin−Ahn addition of vinylmetals to **10** and antiselective addition of cuprates to the pivalate esters). Other examples of oxidative cleavage are discussed in the following sections.

Importantly, though, either configuration of the quaternary carbon in the final carbonyl compound can be accessed by (a) starting from (+)- or (−)-*p*-menthane-3-carboxaldehyde; (b) using only one enantiomer of **10** but accessing either absolute configuration of the alcohol (direct addition of vinylmetals **11** on **10** or $LiBHEt_3$-mediated reduction of ketone **16**); (c) changing the geometry of the double bond; or (d) substituting the cuprate fragment for one of the appendages on the double bond (there are limitations in this case). This constitutes one of the most versatile methodologies in this regard.

Synthesis of an Advanced Intermediate to (−)-Cassiol. (+)-Cassiosside is an antiulcer agent isolated from Chinese cinnamon in 1988 (Scheme 8).[18] (+)-Cassiol is a hydrolysis product of cassioside, which possesses an even higher potency.[18] Several syntheses of cassiol have been reported to date.[19,20] Our methodology offered an efficient solution to the synthesis of cassiol starting from the inexpensive propargyl alcohol. In the

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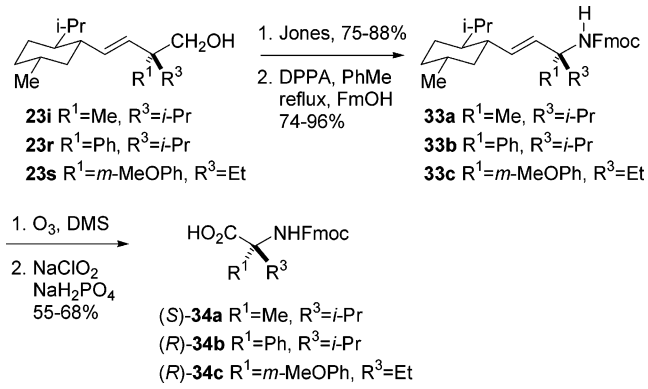
event, the zirconium-catalyzed carboalumination of propargyl alcohol and addition of the resulting vinylalane intermediate to aldehyde **10** furnished diol **12e** (Scheme 8). The primary alcohol was selectively protected to give **12p** in 83% yield for the two steps. The diastereomeric alcohols (10:1 ratio) were chromatographically separated. Pivalate formation and addition of (1-buten-4-yl)cyano cuprate gave a 86% yield of **22l** as a single diastereomer. That adduct underwent a Wacker oxidation using the conditions reported by Smith and co-workers[21] (85%) and the resulting methyl ketone was alkylated to give **29** (53%). Ozonolysis and reductive workup gave an 88% yield of aldehyde **30**. Compound **31**, a molecule closely related to *ent*-**30** has previously been transformed to (+)-cassiol by Taber and co-workers in six steps.[20]

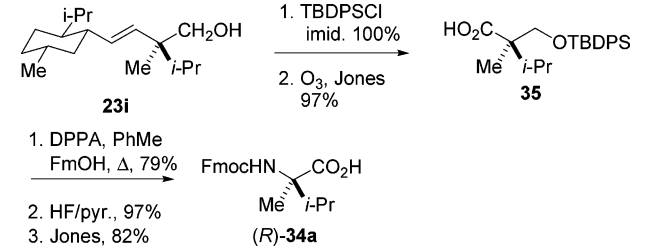
α,α-Dialkylated Amino Acids. Some α,α-dialkylated amino acids are powerful enzyme inhibitors.[22] As part of peptides, α,α-dialkylated amino acids unit may increase metabolic resistance and induce particular conformations resulting in altered properties.[23,24] Their stereoselective synthesis remains a formidable challenge and although many methodologies have been developed over the years, few are general.[25] We promptly realized that cuprate adducts **23i**, **23r**, and **23s** (Table 3, entries 9, 22, and 23), possessing a hydroxymethylene unit could be used to access enantiopure α,α-dialkylated amino acids.[26]

We began by oxidizing the primary alcohol in each alcohol **23** to the corresponding carboxylic acids and transforming the latter into the corresponding carbamates **33a** via a Curtius rearrangement[27] (Scheme 9). Ozonolysis of **33a** and oxidation gave the desired amino acids (*S*)-**34a** in 55% yield. Adducts **23r** and **23s** were converted to (*R*)-**34b** and (*R*)-**34c**, respectively, using the same sequence of reactions (Scheme 9). However, because the alkene in cuprate adducts **22** or **23** can also be transformed into a carboxylic acid unit, the method is stereodivergent. For example, the same intermediate **23i** was converted to the enantiomeric amino acid (*R*)-**34a** by reversing the order of the reactions (Scheme 10). We converted **23i** first to carboxylic acid **35**, which underwent a Curtius rearrangement with the expected retention of stereochemistry. Transforming the hydroxymethylene unit to the carboxylic acid was done using standard reactions. This stereodivergent option raises an already versatile approach to yet another echelon. The combination of carbinol stereochemistry, double-bond geometry, the ability to interchange R^1, R^2, and R^3, and stereodivergence offer at least 16 different ways to access any one enantiomer of amino acid **34** from either enantiomer of *p*-menthane-3-carboxaldehyde. All routes can, in principle, be achieved with excellent control of stereochemistry. In practice, some intermediates with specific double-bond geometries may be more difficult to prepare or some cuprate reagents may not react and so on. However, with such flexibility, the chances of a successful synthesis are significantly raised.

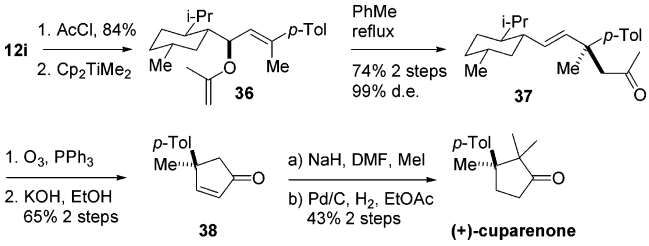
Scheme 9. Route A: Synthesis of α,α-Dialkylated Amino Acid **34a**−**c**



Scheme 10. Route B: Stereodivergent Synthesis of α,α-Dialkylated Amino Acid (*R*)-**34a**



Scheme 11. Synthesis of (+)-Cuparenone



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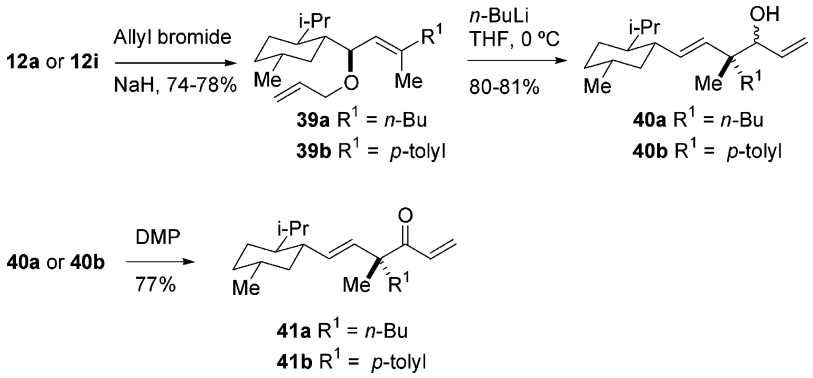
Sigmatropic Rearrangements. Sigmatropic rearrangements provide classic examples of reactions occurring with stereochemical transposition of a chiral center to a distal position.[28] However, the formation of chiral quaternary stereocenters using

Scheme 12. Wittig Rearrangements of **12a** and **12b**



rearrangement reactions is less frequent, presumably because of sensitivity to steric effects.[29] Among reactions capable of chirality transfer from an allylic position, the Claisen rearrangement and its numerous variants is one of the most frequently used methods to generate carbon−carbon bonds with high stereochemical control.[28,30] We were interested to see if chiral alcohols **12a** and **12i** would undergo a Claisen rearrangement and generate in the process a quaternary chiral center.[31] The ortho ester variant of the Claisen rearrangement[32] of alcohol **12i** did not proceed in refluxing toluene or even in neat hot triethyl orthoacetate. These acidic conditions and high temperature led to the decomposition of the starting allylic alcohol. However, acetylation of alcohol **12i** and methylenation of the resulting ester by the Petasis method[33] provided **36**, which underwent a very efficient rearrangement in refluxing toluene to give ketone **37** as a single stereoisomer (Scheme 11). The low temperature at which the rearrangement took place is noteworthy. The diastereomeric purity was checked against an authentic sample of the diastereomer of **37** made from alcohol **13i** (cf. Scheme 3). Ozonolysis of the rearranged product **37** and treatment with base gave cyclohexenone **38**, which was converted to (+)-cuparenone ($[\alpha]_D = +167$ (c 0.15, $CHCl_3$), lit.: −166 (c 0.20, $CHCl_3$) following the method of Meyers.[34]

The [2,3]-Wittig rearrangement[35] has also been used to procure chiral quaternary carbon centers.[36] Alcohols **12a** and **12i** were converted to allyl ethers **39a** and **39b**, respectively, under standard conditions and their rearrangement was effected by treating with *n*-butyllithium at 0 °C (Scheme 12). Products **40a** and **40b** were isolated as mixtures of two inseparable alcohols, in a 3.8:1 ratio in **40a** but the ratio for **40b** was difficult to assess. Nonetheless, we have established the absolute configuration of the major alcohol **40b** to be *R* following conversion to its Mosher ester.[9] It appears that transition-state I having the pendent alkene syn to the less bulky methyl group is favored in accord with expectations (Figure 4).

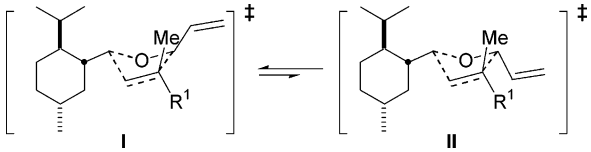


Figure 4. Competing transition states for the [2,3]-Wittig rearrangement of **39**.

The rearrangements were performed with the minor alcohols **13a** and **13i** to acquire authentic samples of the diastereomers (at the quaternary carbon) of **40a** and **40b**, respectively. It was possible to demonstrate, in both cases, that the quaternary center was stereochemically pure by oxidation of the secondary alcohols. Ketones **41a** and **41b** were obtained as single diastereomers by oxidation of **40a** and **40b**, respectively, with Dess−Martin's periodinane.

Conclusions

We have demonstrated the versatility of *p*-menthane-3-carboxaldehyde as a chiral auxiliary to prepare compounds containing a chiral quaternary carbon of high enantiomeric purity. Displacement reactions and rearrangements were efficient in transferring the chirality in most cases. The breadth of structures available by this method is noteworthy but more impressive is the number of possible permutations in the reaction sequence

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or in the substrate/reagent combination allowing one to obtain the desired enantiomer in one of several ways. In amino acids, a stereodivergent approach adds to an already very flexible method. Other extensions of this methodology are underway in our laboratory.

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Supporting Information Available: Experimental and ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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