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Synthesis of 3,4-Disubstituted Piperidines by Carbonyl Ene and Prins Cyclizations: Switching between Kinetic and Thermodynamic Control with Brønsted and Lewis Acid Catalysts

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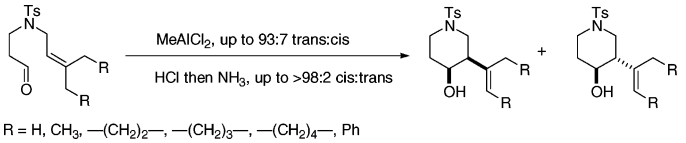

A novel approach to cis and trans 3,4-disubstituted piperidines is described. Carbonyl ene cyclization of aldehydes **4a**−**e** catalyzed by $MeAlCl_2$ in refluxing chloroform afforded the trans piperidines **7a**−**e** with diastereomeric ratios of up to 93:7, while aldehyde **4f** afforded solely the cis product **6f**, which was resistant to isomerization to the trans isomer. It was demonstrated for **4a** that the cyclization catalyzed by a variety of Lewis acids at low temperature proceeded under kinetic control to afford predominantly the cis piperidine **6a**, and this isomerized to the thermodynamically more stable trans piperidine **7a** on warming. In contrast, Prins cyclization of **4a**−**e** catalyzed by concentrated hydrochloric acid in CH_2Cl_2 at low temperature afforded cis piperidines **6a**−**e** with diastereomeric ratios of up to >98:2. The yield and diastereoselectivity of these cyclizations could be improved by using HCl-saturated CH_2Cl_2 to form the corresponding chloride, followed by elimination of HCl effected by ammonia. Aldehydes **4f** and **4g** also cyclized in good yield under the latter conditions. Mechanistic studies supported by DFT calculations (B3LYP/6-31G(d)) suggest that the cyclizations proceed via a mechanism with significant carbocationic character, with the cis carbocation being more stable than the trans carbocation. DFT calculations (B3LYP/6-31G(d)) of the transition state energies for concerted cyclization show that the cis piperidine is also the favored product from cyclization through a more concerted mechanism.

Introduction

Functionalized piperidines occur widely in natural products[1] and synthetic pharmaceuticals. The biological importance of piperidines has led to the development of numerous synthetic approaches to the ring system,[2] but the wide variety of functionality and substitution patterns present in piperidine targets continues to drive the search for new methodologies.[3] In particular, methods for functionalizing the 3-, 4-, and 5-positions of the ring are rather limited. We now report in full the results of our study into the synthesis of 3,4-disubstituted piperidines by carbonyl ene and Prins cyclizations.[4]

The Lewis acid-catalyzed Type I intramolecular carbonyl ene reaction is a very attractive method of ring closure, forming a carbon−carbon bond with the concomitant generation of two contiguous stereocenters.[5] Such reactions are generally limited to the formation of five- and six-membered rings, with the cyclization of citronellal **1** being the prototypical Type I carbonyl ene reaction (Scheme 1). Citronellal cyclizes to give principally the two diastereomeric products **2** and **3**. Diastereoselectivity

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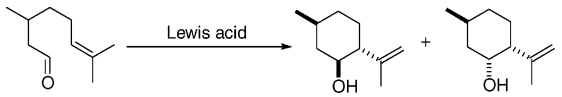
SCHEME 1. Cyclization of Citronellal



is dependent on the particular conditions and Lewis acid used, but generally the trans diastereomer isopulegol **2** is favored, with a diastereomeric ratio of up to 95:5.[6]

Application of the carbonyl ene cyclization to piperidine synthesis has been little explored,[7] and we were interested to see whether the method could be used to synthesize 3,4-disubstituted piperidines.

Results and Discussion

A range of cyclization precursors were straightforwardly synthesized (Scheme 2) from 3-aminopropanol. These were designed to explore the effect of steric bulk and the nucleophilicity of the ene component in the cyclization reaction.

N-Tosylation[8] (94%) followed by *N*-alkylation with the corresponding allylic bromide (59−86%) afforded the alcohols **4a**−**g** in excellent overall yields. Subsequent oxidation was generally carried out with PCC, but in the case of alcohol **1c**, trace formation of piperidinone **5** via the competing tandem oxidation−cyclization−oxidation reaction[9] led us to use substoichiometric amounts of TPAP with NMO as reoxidant.[10] This avoided the side reaction, and aldehydes **4a**−**g** were prepared in 57−83% yields after flash column chromatography. These β-amino aldehydes were generally used immediately, but they could be stored for several weeks at −20 °C without significant decomposition.

Our initial investigation focused on the carbonyl ene reaction of substrate **4a** to afford the diastereomeric piperidines **6a** and **7a**, catalyzed by $MeAlCl_2$. This Lewis acid has previously been shown to be effective at catalyzing carbonyl ene reactions to form six-membered rings,[11] and our investigation focused on the effect of temperature, time, and amount of catalyst on diastereoselectivity (Table 1).

Conversion of **4a** to the diastereomeric piperidines **6a** and **7a** was rapid and high yielding, with isolated yields of the crude piperidine mixtures typically in excess of 90%. The reaction was facile at −78 °C, even with substoichiometric amounts of the Lewis acid (entries 1−4). At this temperature, the major product was cis diastereomer **6a**, and the diastereomeric ratio proved to be relatively insensitive to the amount of Lewis acid used. Raising the temperature at which the reaction was performed to 25 °C and quenching after 2 h again gave **6a** as the major product (entry 5). Increasing the amount of Lewis acid and the reaction time at this temperature resulted in preferential formation of trans diastereomer **7a** (entries 6 and 7), suggesting that under these conditions the carbonyl ene reaction is reversible and that **6a** is the kinetic product, equilibrating to **7a** on warming. This was confirmed by raising the temperature to 61 °C (entry 8); under these conditions, **7a** predominated, with a diastereomeric ratio of 92:8 **7a**:**6a**. This product ratio was also reached by subjecting a sample of **6a** to the same equilibrating reaction conditions.[12]

Along with the two major products, trace amounts (<5%) of the cis chloride **8a** were also isolated (for stereochemical assignment vide infra). Such γ-chloro alcohols have been reported previously as byproducts in alkylaluminum chloride Lewis acid-catalyzed carbonyl ene reactions.[13,14] This side product was difficult to separate from **6a** chromatographically, but simply stirring a THF solution of a mixture of **6a** and **8a** with aqueous ammonia in THF induced an elimination to afford essentially quantitative recovery of pure **6a** (Scheme 3).

The diastereomers were readily separated on silica to afford pure **6a** and **7a** as white crystalline solids. The ^{1}H NMR spectrum of **7a** exhibited a trans diaxial coupling constant of 10.1 Hz between the C3−C4 ring protons, and the trans relationship between the two substituents was confirmed by X-ray analysis. Coupling constants could not be extracted from the ^{1}H NMR spectrum of **6a**, but it also proved possible to grow single crystals of this diastereoisomer, and X-ray analysis confirmed the cis relationship between the two substituents.

Other Lewis acids were screened at low temperature in an effort to favor formation of the kinetic product **6a** (Table 2).

Aluminum trichloride, which is more Lewis acidic than $MeAlCl_2$, was found to be an effective catalyst and favored formation of the kinetic product **6a** (entries 1−3). In contrast, $FeCl_3$ afforded only trace amounts (<5%) of the products (entry 4), with the remainder of the starting material returned unchanged. Tin tetrachloride was effective at catalyzing the reaction but the diastereoselectivity was poor (entry 5). Titanium tetrachloride, on the other hand, was found to be an extremely effective catalyst (entry 6), favoring the kinetic product with a high diastereoselectivity, but also leading to the formation of

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SCHEME 2. Synthesis of Cyclization Precursors

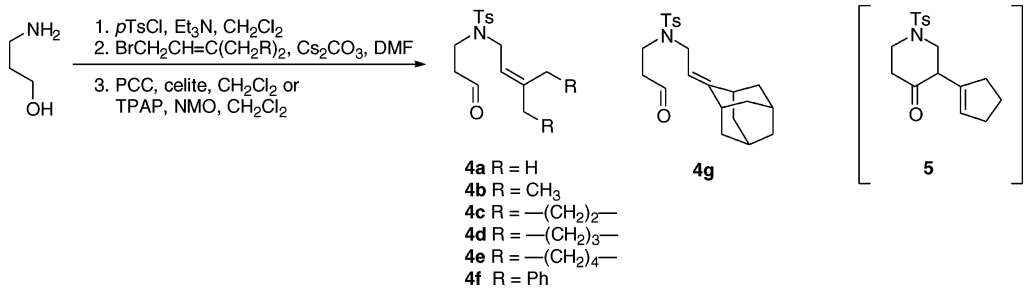
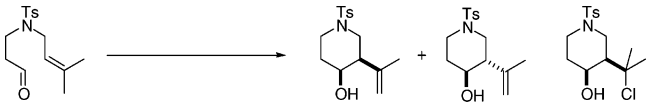


TABLE 1. Cyclizations of Aldehyde 4a with $MeAlCl_2$



entry	equiv of $MeAlCl_2$[a]	temp (°C)	time (h)	**6a**:**7a**[b]
1	0.15	−78	8	67:33
2	0.3	−78	8	70:30
3	0.5	−78	8	67:33
4	1.0	−78	7	73:27
5	0.08	25	2	67:33
6	0.3	25	16	33:67
7	0.5	25	20	17:83
8	1.0	61[c]	16	8:92

[a] All reactions were performed in dry CH_2Cl_2 unless otherwise stated. [b] The ratio was determined by integration of crude ^1H NMR spectra. [c] The reaction was performed in dry chloroform.

SCHEME 3. Elimination of HCl from Chloride 8a

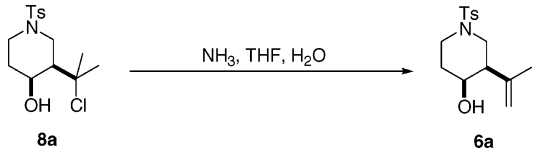


TABLE 2. Cyclization of Aldehyde 4a with a Variety of Lewis Acids

entry	Lewis acid[a]	equiv	time (h)	**6a**:**7a**[b]
1	$AlCl_3$	0.1	7	83:17
2	$AlCl_3$	0.3	7	83:17
3	$AlCl_3$	0.5	6	75:25
4	$FeCl_3$	0.5	7	trace
5	$SnCl_4$	0.5	7	67:33
6	$TiCl_4$	0.5	17	92:8
7	$ZnBr_2$	0.5	7	no reaction[c]
8	$Sc(OTf)_3$	0.5	7	50:50
9	$Cu(OTf)_2$	0.5	7	no reaction[c]
10	$Yb(OTf)_3$	0.5	7	no reaction[c]
11	$BF_3{\cdot}Et_2O$	0.5	7	67:33

[a] Reactions were performed in CH_2Cl_2 at −78 °C. [b] The ratio was determined by integration of ^1H NMR of the crude mixture of piperidines. [c] Starting material was recovered.

significant amounts of the cis chloride **8a**; the amount formed varied between runs, but was typically between 20% and 40%.

Exploration of zinc bromide and a range of metal triflates met with limited success (entries 7−10), with only scandium triflate catalyzing the reaction with a surprising lack of selectivity. Boron(III) fluoride etherate gave **6a** and **7a** with poor diastereoselectivity, along with up to 75% of the cis fluoride, the fluoro analogue of chloride **8a**. The stereochemistry of the fluoride was assigned by comparison of the NMR spectra of the two compounds.

TABLE 3. Cyclization of Aldehydes 4a−g with $MeAlCl_2$

entry	aldehyde[a]	time (h)	**6**:**7**[b]	yield (%)[c]
1	**4a**	16	8:92	74 (6)
2	**4b**	35	22:78	55 (15)
3	**4c**	27	30:70	53 (22)
4	**4d**	27	7:93	74 (4)
5	**4e**	27	25:75	61 (20)
6	**4f**	27	>98:2	90
7	**4g**	27		no reaction[d]

[a] Reactions were performed with 1 equiv of $MeAlCl_2$ in chloroform at 61 °C. [b] The ratio was determined by integration of ^1H NMR of a crude mixture of piperidines. [c] Isolated yields of major (minor) isomers following chromatography. [d] Starting material was recovered.

Cyclization of the remaining aldehydes **4b−g** was studied under the optimized $MeAlCl_2$ conditions; the results are shown in Table 3.

Analysis of the products **6b** and **7b** from cyclization of **4b** was complicated by the presence of *E* and *Z* double bond isomers, and so the diastereomeric ratio was verified after hydrogenation to the saturated products (entry 2). Aldehydes **4c−e**, in which the alkene is exocyclic to a five-, six-, and seven-membered ring, respectively, likewise all favored the trans diastereoisomer (entries 3−5), a preference that was particularly marked in the case of the cyclohexyl system (entry 4).

Surprisingly, **4f** cyclized to give exclusively the cis piperidine **6f**, identified from the characteristic coupling pattern of the C-4 proton. Only one double bond isomer was present, and an X-ray crystal structure revealed this to be the *Z*-isomer.

The adamantyl substrate **4g** did not undergo the carbonyl ene cyclization with $MeAlCl_2$, returning only unreacted starting material. Aldehyde **4g** would not be expected to undergo a concerted cyclization as this would lead to formation of a bridgehead double bond, compounds **11** and **12**, in violation of Bredt's rule.[15] Cyclization could be possible via a more stepwise pathway (Scheme 4), but none of the products that could come from the intermediacy of cations **9** and **10** was observed, e.g., interception by a nucleophile to afford **13** and **14**.

Brønsted Acid-Catalyzed Reactions. Closely related to the carbonyl ene reaction is the Prins reaction, the addition of an aldehyde to an alkene catalyzed by a Brønsted acid.[16] Reports of intramolecular Prins reactions to form six-membered rings are less common than their carbonyl ene counterparts, but we were intrigued by a report from Holker of a highly diastereoselective example catalyzed by HCl.[17] A small number of Brønsted acids were therefore screened for the cyclization of **4a** (Table 4).

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SCHEME 4

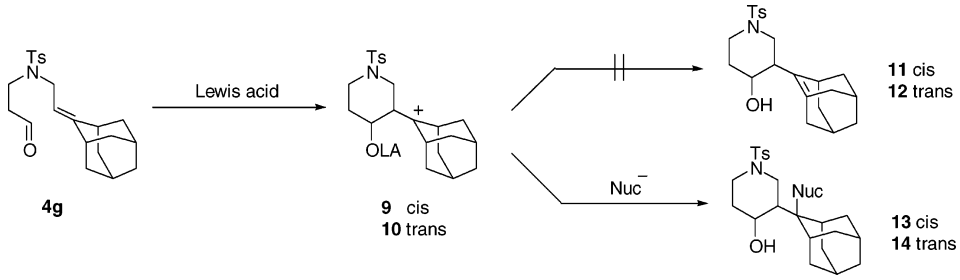


TABLE 4. Cyclization of 4a with a Variety of Brønsted Acids

entry	Brønsted acid[a]	equiv	temp (°C)	time (h)	**6a**:**7a**[b]
1	CF_3SO_3H	0.5	−78	8	78:22
2	TsOH	0.5	−78	7	no reaction[c]
3	HCl[d]	3.0	−78	16	95:5
4	HCl[d]	1.0	−78	64[e]	93:7
5	HCl[d]	3.0	61[f]	16	86:14
6	HBr[g]	3.0	−78	18	92:8
7	HI[h]	3.0	−78	20	90:10
8	H_2SO_4[i]	3.0	−78	16	87:13

[a] All reactions were performed in CH_2Cl_2 unless otherwise stated. [b] The ratio was determined by integration of ^{1}H NMR of a crude mixture of piperidines. [c] Starting material was recovered. [d] Refers to concentrated (37%) hydrochloric acid. [e] The reaction was only 80% complete after this time. [f] The reaction was performed in chloroform. [g] Refers to 48% hydrobromic acid. [h] Refers to 57% hydriodic acid. [i] Refers to concentrated sulfuric acid.

Results were disappointing with trifluoromethanesulfonic acid and *p*-toluenesulfonic acid (entries 1 and 2), but hydrochloric acid proved to be an extremely effective catalyst for the Prins cyclization of **4a**. Three equivalents of concentrated HCl at −78 °C in CH_2Cl_2, conditions presumed to lead to a low concentration of HCl in CH_2Cl_2, effected cyclization to **6a** and **7a** with a diastereomeric ratio of 95:5 in favor of the kinetic isomer **6a** (entry 3). A trace (<5%) of chloride **8a** was produced under these conditions, which could be easily eliminated as before to afford pure **6a**. Reducing the amount of acid led to an unacceptably slow reaction without improvement in the diastereomeric ratio (entry 4). Although raising the temperature of the reaction lowered the diastereoselectivity, the cyclization still favored cis product **6a** (entry 5). Hydrobromic acid and hydriodic acid were also effective catalysts, but the diastereoselectivity of these reactions was not better than that with hydrochloric acid (entries 6 and 7), and there were also traces (<5%) of a side product produced under these conditions, presumably the γ-bromo and γ-iodo alcohols.

Somewhat surprisingly, the diastereoselectivity with concentrated sulfuric acid in CH_2Cl_2 (entry 8) was relatively modest compared to the results with HCl (entry 3). Switching to dilute sulfuric acid (0.05 M aqueous, no cosolvent), cyclization proceeded very slowly at room temperature (176 h) to give a mixture of **6a**, **7a**, and the diols **15** and **16** with a ratio of 15:8:54:23, respectively, i.e., a 69:31 ratio of cis:trans products (Scheme 5).

Diol **15** was the major product and was isolated in 51% yield. Increasing the reaction temperature to 50 °C improved the rate of reaction (reaction complete in 19 h), and also led to increased amounts of the alkene products (a 25:13:44:18 mixture of **6a**:**7a**:**15**:**16**), although the overall cis:trans ratio remained unchanged at 69:31. It is likely that under the conditions of elevated temperature, dehydration of the tertiary alcohols takes place to give the alkenes.

TABLE 5. Cyclization of Aldehydes 4a−g with Concentrated Hydrochloric Acid

entry	aldehyde[a]	time (h)	**6a**:**7a**[b]	yield (%)[c]
1	**4a**	16	95:5	79 (4)
2	**4b**	16	>98:2	86
3	**4c**	16	90:10	71 (7)
4	**4d**	16	89:11	72 (9)
5	**4e**	16	80:20	62 (14)
6	**4f**	16		no reaction[d]
7	**4g**	16		no reaction[d]

[a] Reactions were performed with 3 equiv of concentrated (37%) hydrochloric acid in CH_2Cl_2 at −78 °C. [b] The ratio was determined by integration of ^{1}H NMR of a crude mixture of piperidines. [c] Isolated yields of major (minor) isomers following chromatography. [d] Starting material was recovered.

TABLE 6. Cyclization of Aldehydes 4a−e in CH_2Cl_2 Saturated with HCl

entry	aldehyde[a]	time (h)	**6**:**8**:**7**[b]	**6**:**7** after elim[b]	yield (%)[c]
1	**4a**	2	57:40:3	97:3	75 (1)
2	**4a**	6	4:93:3		
3	**4b**	2	54:45:1	>98:2	80 (0)
4	**4b**	6	47:52:1		
5	**4c**	2	89:6:5	95:5	83 (4)
6	**4c**	6	80:8:12		
7	**4d**	2	97:3:0	>98:2	70 (0)
8	**4d**	6	86:6:8		
9	**4e**	2	94:6:0	>98:2	87 (0)
10	**4e**	6	82:14:4		

[a] Reactions were performed in CH_2Cl_2 saturated with HCl at −78 °C. [b] The ratio was determined by integration of ^{1}H NMR of a crude mixture of piperidines. [c] Isolated yields of **6** (**7**) following chromatography.

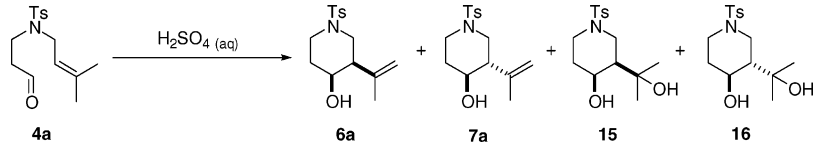
All four products were readily separated on silica to afford the pure compounds as white crystalline solids. The ^{1}H NMR spectrum of **16** identified a coupling constant of 10.5 Hz between the C3−C4 ring protons, which is consistent with trans diaxial coupling, while X-ray analysis of single crystals of **15** confirmed the cis relationship between the two substituents.

The remaining aldehydes **4b−g** were cyclized under the optimized concentrated hydrochloric acid conditions; the results are shown in Table 5.

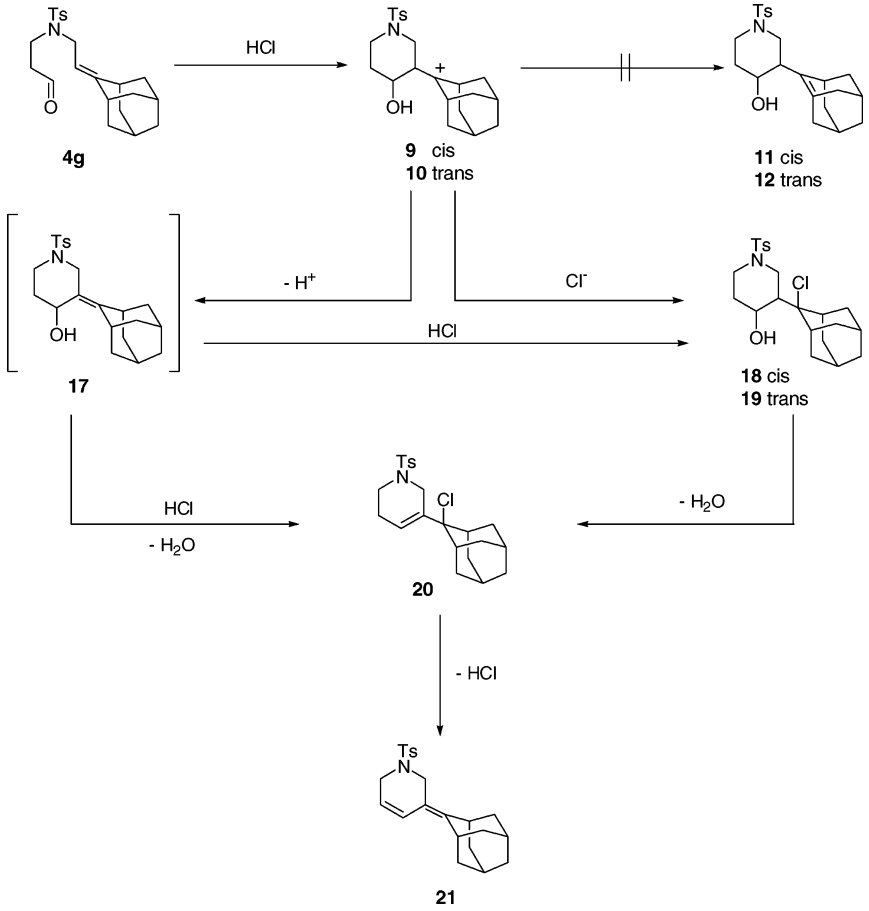
Cyclization of **4b** exhibited a remarkable diastereoselectivity of at least 98:2, with no trans product detectable by NMR; as before, a mixture of double bond isomers was produced and the diastereomeric ratio was verified both before and after hydrogenation. Paralleling our earlier findings, around 5% of the chloride resulting from addition of HCl to the double bond of **6b** was also obtained; subjecting a THF solution of the chloride to aqueous ammonia effected elimination to the alkene.

Extending our study to aldehydes **4c−e**, the preference for formation of the cis diastereoisomers **6c−e** was again marked (entries 3, 4, and 5), although not as high as the acyclic examples. Aldehyde **4f** failed to give any cyclization products,

SCHEME 5. Cyclization of Aldehyde 4a in Dilute Sulfuric Acid



SCHEME 6. Cyclization and Rearrangement of Aldehyde 4g



with only starting material recovered. The addition of more acid and prolonged reaction times simply resulted in the formation of decomposition products.

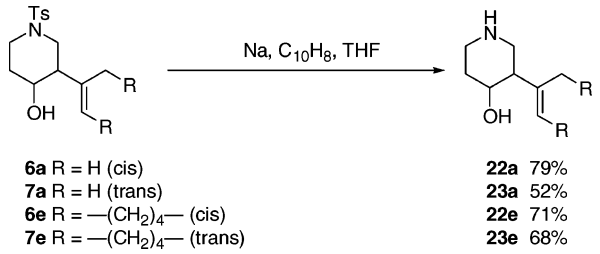
Adamantyl compound **4g** also failed to cyclize under these conditions. Although the concerted cyclization pathway is not open to **4g** (vide supra), we had hoped that under Brønsted acid conditions a Prins-type cyclization could occur via generation and trapping of the cations **9** and **10**.

The successful results obtained with concentrated hydrochloric acid led us to explore the cyclization of **4a** in dichloromethane saturated with hydrogen chloride gas. Initially the reaction was performed by bubbling anhydrous HCl gas through a −78 °C CH_2Cl_2 solution of **4a** for 30 min, followed by stirring for a further 2 h at this temperature. This led to a 57:3:40 mixture of **6a**:**7a**:**8a** (i.e. 97:3 cis:trans), while in a separate experiment, extending the reaction time to 6 h gave a 4:3:93 mixture of **6a**:**7a**:**8a** (i.e. 97:3 cis:trans). No trans chloride was detected in the crude NMR spectrum or in any of the fractions isolated on purification.

Although the latter experiment led to chloride **8a** being the major product, it was difficult to isolate a pure sample of **8a** as it readily eliminated HCl on silica to give **6a**, and **8a** could not be crystallized away from **6a** and **7a**. However, **7a** could be easily separated from **6a** and **8a** chromatographically, so the mixture of **6a** and **8a** isolated after purification was subjected to HCl-saturated CH_2Cl_2 for a further 2 h to give a 3:97 mixture of **6a**:**8a** in an overall yield of approximately 75% from **4a**; the structure of **8a** was confirmed by X-ray crystallography. Cyclization of the remaining aldehydes in HCl-saturated CH_2Cl_2 led smoothly to the expected piperidines with excellent diastereoselectivities in favor of cis products (Table 6). The best diastereoselectivities were obtained after 2 h at −78 °C; extending the reaction time to 6 h led unsurprisingly to increased amounts of the corresponding cis chloride, but also to a slight decrease in the overall cis:trans ratio in most cases. Once again, trans chloride products were not detected.

Unlike the previous example, it was not possible to drive the cis alkenes **6b**−**e** completely to the corresponding cis chlorides, possibly as a result of the greater steric hindrance present in these systems. Instead, the crude mixture of cis and trans alkenes and cis chloride was subjected directly to aqueous ammonia−THF to effect elimination of HCl from the chloride, leaving only the separable alkene products. This proved to be a very efficient way of synthesizing the cis alkenes **6a**−**e** in good overall yields and with much improved diastereoselectivity over the concentrated hydrochloric acid conditions.

SCHEME 7. Removal of the *p*-Toluenesulfonyl Protecting Group



6a R = H (cis) **22a** 79%
7a R = H (trans) **23a** 52%
6e R = —$(CH_2)_4$— (cis) **22e** 71%
7e R = —$(CH_2)_4$— (trans) **23e** 68%

Cyclization of **4f** for 2 h at −78 °C in HCl-saturated CH_2Cl_2 afforded exclusively the cis piperidine **6f**, again as the *Z* double bond isomer. Prolonged acid treatment and warming to room temperature did not yield any of the chloride, presumably because elimination to form the conjugated alkene is very facile.

Pleasingly, adamantyl system **4g** also underwent a facile cyclization in HCl-saturated CH_2Cl_2. After 2 h at −78 °C all of the starting material had been consumed, and three products were visible in the crude ^{1}H NMR, cis and trans chlorides **18** and **19** in a 52:23 ratio, along with 25% of chloroalkene **20**. X-ray crystal structures confirmed the identity of **18** and **19**.

Extending the reaction time to 6 h at −78 °C led to an erosion in the cis:trans selectivity to 42:36, with the remaining 22% of the material being **20**. To confirm that the cis chloride **18** could isomerize to the trans chloride **19** a pure sample of **18** was subjected to HCl-saturated CH_2Cl_2 at −78 °C for 24 h to give a 60:40 ratio of **18**:**19**.

Repeating the cyclization for 6 h at room temperature gave a similar amount of the chlorides **18** and **19**, but with the trans chloride predominating (34:44 ratio of **18**:**19**), while the amount of **20** decreased slightly to 18%, and 4% of a new product was present, identified as the diene **21**. Extending the reaction time to 24 h at room temperature resulted in an increase in the trans: cis ratio for the chlorides, along with increased amounts of the diene **21**. Both chloro alcohols were unstable toward decomposition to the diene on storage, with traces of the latter evident after a few days in the refrigerator.

It is assumed that cyclization proceeds via the cis and trans cations **9** and **10**, with trapping by chloride ion leading to **18** and **19** (Scheme 6). The alternative pathway involving loss of a proton from the adamantyl ring would afford bridgehead alkenes **11** and **12**, in violation of Bredt's rule. The product resulting from loss of a proton from the piperidine ring, **17**, is not observed either, presumably due to the significant $A^{1,3}$ strain present in this molecule, although it cannot be ruled out as an intermediate in the formation of **20** or chlorides **18** and **19**. Acid-catalyzed elimination of water from **18** and **19** affords **20**, the main side product in the low-temperature cyclization, and loss of HCl gives the diene **21**.

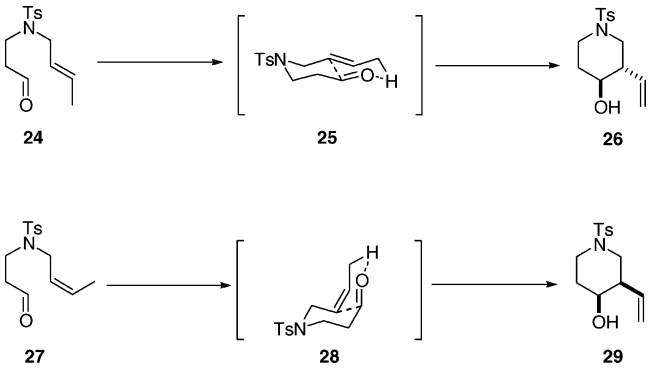
Removal of the *p*-Toluenesulfonyl Protecting Group. Removal of the *p*-toluenesulfonyl protecting group was carried out on a representative range of examples by stirring the *N*-tosylpiperidines with 6 equiv of sodium naphthalenide in THF at −78 °C (Scheme 7). Deprotection proceeded cleanly to afford good yields (52−79%) of the piperidines **22** and **23**, although the loss of a small amount of material on aqueous workup was unavoidable due to the polar nature of the deprotected products.

Mechanistic Considerations. Carbonyl ene cyclizations to form six-membered rings typically favor the thermodynamically more stable stereoisomer. Considering the cyclization of citronellal, one of the most well-studied examples, the thermodynamically more stable trans isomer isopulegol **2** is favored with a variety of Lewis acids.[6] There is no evidence that cyclization proceeds through a kinetic intermediate that isomerizes. Indeed, Nakatani demonstrated that under the conditions of zinc bromide in benzene, the cyclization of citronellal to afford chiefly isopulegol **2** is irreversible.[6a] More recently, however, Kočovský has shown that several Lewis acids, including zinc chloride in dichloromethane, rapidly isomerize neoisopulegol **3** to isopulegol **2**.[18]

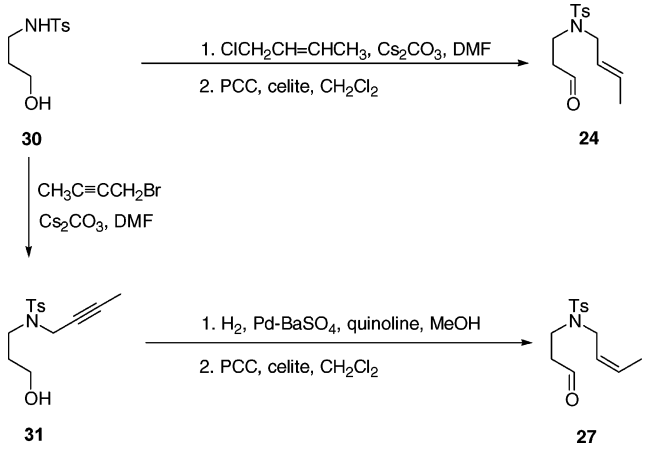
A reversal in the sense of diastereoselectivity of citronellal cyclization to favor the cis-diastereoisomer neoisopulegol **3** (dr 75:25) has been achieved with Wilkinson's catalyst, although this observation has not been satisfactorily explained.[19] Koèovsk×c6 has explored the cyclization with bulky molybdenum Lewis acids, observing a cis:trans ratio of up to 80:20. In this case it is suggested that the bulky Lewis acid forces cyclization through a boatlike transition state, leading to the switch in diastereoselectivity.[18]

Given this precedent for citronellal, our cyclization results for aldehydes **4a**−**e** using Lewis acids under the equilibrating conditions of elevated temperature were unsurprising and readily explained by the accepted concerted cyclization mechanism. The strong preference for formation of the kinetic product under Brønsted acid conditions, or with Lewis acids at low temperature, was much more difficult to account for, and did not appear to fit with the classical concerted mechanism. Likewise, it was

SCHEME 8. Transition States for Concerted Cyclizations of 24 and 27



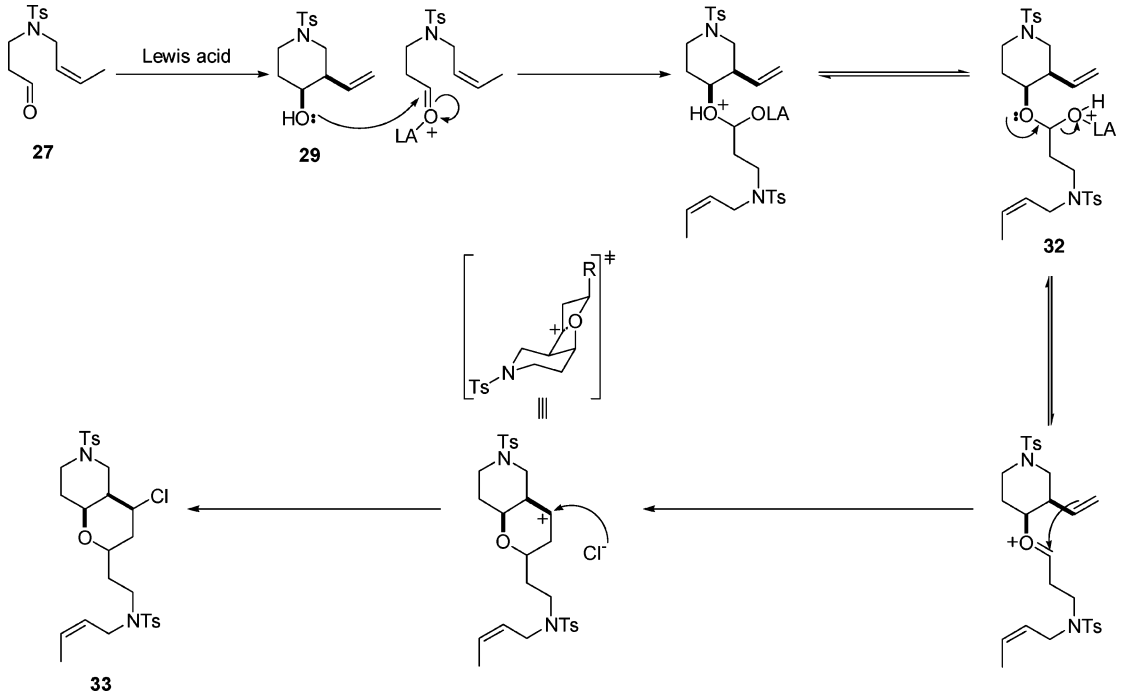
SCHEME 9. Synthesis of Aldehydes 24 and 27



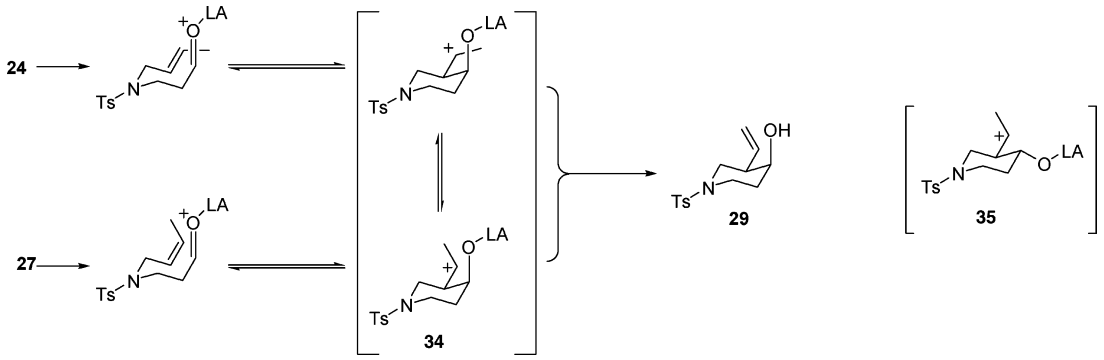
(18) Kočovský, P.; Ahmed, G.; Srogl, J.; Malkov, A. V.; Steele, J. *J. Org. Chem.* **1999**, *64*, 2765−2775.

(19) Funakoshi, K.; Togo, N.; Koga, I.; Sakai, K. *Chem. Pharm. Bull.* **1989**, *37*, 1990−1994.

SCHEME 10. Proposed Dimerization Leading to 33



SCHEME 11. Proposed Reaction Pathway



difficult to rationalize the preference of **4f** to give exclusively this cis product **6f** with $MeAlCl_2$ in refluxing chloroform.

It was hoped that the cis and trans crotyl substrates **24** and **27** would provide a probe for the cyclization mechanism. We reasoned that if the cyclizations proceeded through a concerted mechanism, then the *E*-crotyl aldehyde **24** would be expected to afford the trans piperidine **26** via transition state **25**, while the *Z*-crotyl aldehyde **27** would afford the cis piperidine **29** via transition state **28** (Scheme 8). The synthesis of both aldehydes was straightforward (Scheme 9).

Alkylation of **30** with commercially available crotyl chloride (approximately 5:1 *E*:*Z*) gave the corresponding crotyl alcohol with an *E*:*Z* ratio of 3:1. The stereoisomers were inseparable, and so the mixture was oxidized with PCC to give aldehyde **24**, also as a 3:1 *E*:*Z* mixture. To prepare the *Z*-isomer, **30** was alkylated with 1-bromo-2-butyne to give alkyne **31**, which underwent smooth reduction on treatment with hydrogen and $Pd-BaSO_4$ poisoned with quinoline to afford the *Z*-crotyl alcohol (20:1 *Z*:*E*). PCC oxidation afforded the *Z*-crotyl aldehyde **27** with an unchanged *Z*:*E* ratio.

With both cyclization precursors in hand we explored their cyclization under Lewis and Brønsted acid conditions. Neither **24** nor **27** would undergo a Prins-type reaction under our previously optimized conditions of 3 equiv of HCl at −78 °C in CH_2Cl_2, even with extended reaction time. Increasing the reaction temperature to 25 °C again failed to result in any reaction after 5 days. Even subjecting the two substrates to the much more vigorous conditions of HCl-saturated CH_2Cl_2 at room temperature failed to result in any reaction, giving after 25 h recovery of aldehyde starting materials. Extending the reaction time to 80 h under these conditions gave rise to extensive decomposition.

It appeared that removal of a methyl group from **4a** to give **24** and **27** had completely deactivated the system toward Prins cyclization. Since the Prins reaction is generally believed to proceed through a stepwise mechanism via a cationic intermediate,[16] the lack of reactivity of the *E* and *Z* crotyl compounds under these conditions could be accounted for by their reluctance to react through a much less favorable secondary carbocation (cf. tertiary carbocation for substrate **4a**). We therefore turned our attention to the Lewis acid-catalyzed reactions of **24** and **27**.

Both **24** and **27** proved to be completely unreactive at −78 °C with the Lewis acids that had previously been shown to be effective at catalyzing the cyclization of **4a**, but reaction occurred on raising the temperature to 25 °C. Treatment of **24**

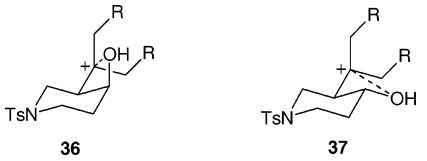


FIGURE 1. Overlap with the oxygen lone pair stabilizes the cis cation **36**.

and **27** with 0.5 equiv of $MeAlCl_2$ at 25 °C led in both cases to the formation of two products that were readily separable on silica. The minor product, formed in around 20% yield in each case, was the desired piperidine, and comparison of the ^1H NMR spectrum with those of **6a** and **7a** clearly revealed it to be the cis diastereomer **29**; no trans diastereomer was detected in the crude reaction mixture from either reaction.

The major product from the reaction had a very complex ^1H NMR spectrum, suggesting that it was a mixture of diastereoisomers. It was apparent that there were resonances from more than one tosyl group and there were also resonances from more than one alkene. The product had a molecular weight of 580, and the mass spectrum showed an isotope pattern characteristic of one chlorine atom. Following extensive 2-D NMR we tentatively assigned the structure **33** to this product, and propose that it is formed via the dimerization process shown in Scheme 10. Dimerization is shown starting from **27**, although an identical pathway is assumed to operate for **24**.

Due to the less electron-rich disubstituted double bond, the rate of intramolecular cyclization is reduced, allowing intermolecular reactions to compete. Dimerization to form a hemiacetal of the type **32** is followed by Lewis acid-catalyzed oxonium ion formation, and cyclization to a pyran as shown. There are 16 possible stereoisomers of **33**, and we believe at least four of these are present in the mixture, making it impossible to unequivocally assign a structure to this compound. The formation of pyrans has been observed previously as a side reaction competing with intermolecular ene reactions.[6b]

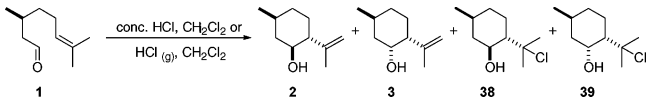
With $AlCl_3$, $FeCl_3$, and $SnCl_4$ **33** was the sole product of the reaction, and so we sought to optimize the formation of piperidine **29** with $MeAlCl_2$. Performing the reaction at higher dilution (1 mM in **24** or **27** compared to 20 mM in the earlier runs) increased the yield of **29**, but at the expense of considerably increased reaction times. Happily, the use of 3 equiv of $MeAlCl_2$ at a 10 mM concentration of either substrate led to an 85:15 mixture of **29**:**33**, with a 68% isolated yield of **29**. Surprisingly, *both* substrates gave solely the cis piperidine; no trans isomer was detectable.

The fact that both substrates afforded the cis piperidine suggested that the reaction was not concerted, but proceeded with significant stepwise character (Scheme 11).

The rate-determining step is likely to be the C−C bond-forming step involving attack of the alkene on the activated aldehyde, and the strong preference for formation of the cis product suggests a lower energy pathway for the formation of the cis carbocation **34** compared with the trans carbocation **35**.

Our results for aldehydes **4a**−**f** suggest that under Brønsted acid catalysis these too cyclize via a pathway with significant stepwise character. In the cis cation **36**, overlap between the oxygen lone pair and the empty p-orbital at the cationic center could provide a stabilizing interaction (Figure 1). Such overlap is geometrically unfavorable in the case of the trans cation **37**. The cyclization catalyzed by $MeAlCl_2$ is more concerted, although the preference to form the cis product at low temperature suggests that there is significant cationic character to the transition state. When **4a** is cyclized in aqueous sulfuric acid the overall cis:trans ratio is a more modest 2:1, suggesting that the energy difference between the cis and trans cations is reduced as a result of solvation by the surrounding water molecules.[20]

SCHEME 12. Cyclization of Citronellal with HCl



In the case of the crotyl aldehydes **24** and **27**, the loss of a methyl group makes the resulting secondary cations (or any cationic character developed during cyclization through a more concerted pathway) much less stable than **36** and **37**. As a consequence, the stabilizing interaction with the oxygen lone pair becomes even more significant, and cyclization through the trans cation is energetically inaccessible. In a similar way, the two-electron withdrawing aryl substituents present in **4f** serve to destabilize the trans cation relative to the cis cation, leading to exclusive formation of the cis piperidine **6f**.

As a reference point we performed the cyclization of citronellal under our optimal hydrochloric acid conditions to give a 16:33:11:40 mixture of **2**:**3**:**38**:**39** (Scheme 12).

Interestingly, the cyclization favored formation of the cis products **3** and **39**, but in marked contrast to our own system, the combined ratio of cis:trans products was only 73:27. Using HCl-saturated CH_2Cl_2 at −78 °C afforded after 4 h an 80:20 mixture of **39**:**38** as the sole products.[21] Repeating the reaction at room temperature while keeping the reaction time at 4 h led to a 67:33 mixture of **39**:**38** as the sole products.

These results for citronellal under Brønsted acid catalysis, conditions likely to result in a much more stepwise pathway, would also appear to be consistent with the cation stability arguments laid out above. The much higher diastereoselectivity for the cyclization of aldehydes of the type **4** would therefore suggest that there is a larger energy difference between cis and trans cations **36** and **37** compared with the cis and trans cations generated during the cyclization of citronellal, possibly as a result of the electron withdrawing inductive effect of the *N*-tosyl substituent.

In an attempt to quantify the differences in cation stability, we calculated the structures and relative stabilities of the cis and trans cations derived from **4a** and those derived from citronellal at the B3LYP/6-31G(d) level of theory. The structures of these cations are shown in Figures 2 and 3.

In the case of the cis and trans cations derived from citronellal, the energy difference between the geometry-optimized structures is 0.19 kcal in favor of the trans cation. This difference is clearly at odds with the observed diastereoselectivity. However, comparison with the corresponding cations derived from **4a** is instructive. The stability of the two cations derived from **4a** (Figure 2b) is reversed, with the cis cation being more stable that the trans cation by 0.82 kcal. Although this energy

(20) The cyclization of citronellal in aqueous sulfuric acid and in micelles has been studied. In both cases a preference for cis products is reported. See: (a) Zimmerman, H. E.; English, J. *J. Am. Chem. Soc.* **1953**, *75*, 2367−2370. (b) Clark, B. C.; Chamblee, T. S.; Iacobucci, G. A. *J. Org. Chem.* **1984**, *49*, 4557−4559.

(21) Similar levels of diastereoselectivity have been reported for the cyclization of citronellal with Et_3N−5HF to form the analogous fluorides. See: Hayashi, E.; Hara, S.; Shirato, H.; Hatakeyama, T.; Fukuhara, T.; Yoneda, N. *Chem. Lett.* **1995**, 205−206.

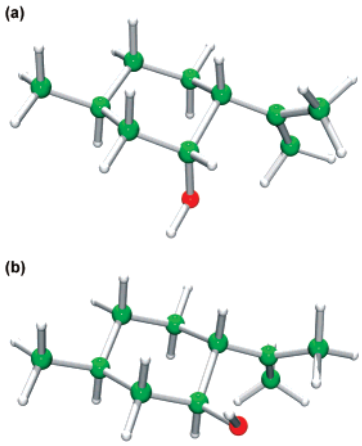


FIGURE 2. Calculated (B3LYP/6-31G(d)) structures of (a) the cis cation derived from citronellal and (b) the trans cation derived from citronellal. Carbon atoms are green, oxygen atoms are red, and hydrogen atoms are white.

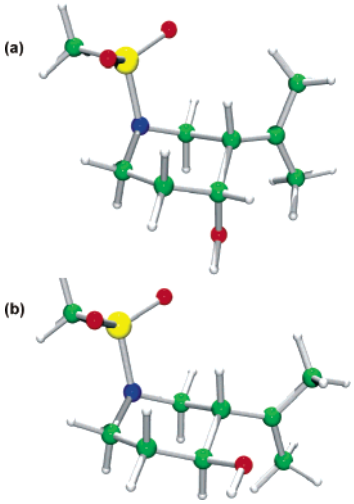


FIGURE 3. Calculated (B3LYP/6-31G(d)) structures of (a) the cis cation derived from compound **4a** and (b) the trans cation derived from compound **4a**. Carbon atoms are green, oxygen atoms are red, nitrogen atoms are blue, sulfur atoms are yellow, and hydrogen atoms are white.

difference is too small to explain the absolute diastereoselectivities observed in this system, these results suggest that, if cation stability is a factor, then the reaction involving **4a** would be expected to be markedly more cis selective than that involving citronellal.

Recognizing that the reaction pathways may be more concerted under Lewis acidic conditions we calculated the transition states for the concerted processes involving citronellal and compound **4a** at the B3LYP/6-31G(d) level of theory. The calculated transition states are shown in Figures 4 and 5.

Although the actual activation barriers in the absence of Lewis acid are very high, the structures and relative energies of these transition states are instructive. In the case of citronellal, the energy difference between the cis and trans concerted transition states is 0.78 kcal in favor of the trans transition state. In the case of compound **4a**, the cis transition state is more stable by 0.79 kcal. These results suggest that even if the reaction has some concerted character, the preference for a much more cis selective process in the case of compound **4a** when compared to citronellal would be maintained.

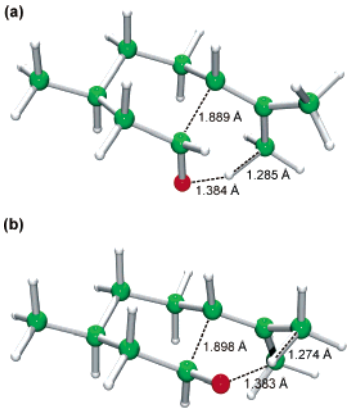


FIGURE 4. Calculated (B3LYP/6-31G(d)) structures of (a) the cis transition state derived from citronellal and (b) the trans transition state derived from citronellal. Carbon atoms are green, oxygen atoms are red, and hydrogen atoms are white.

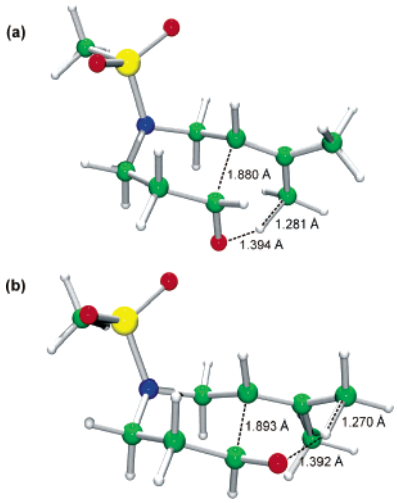


FIGURE 5. Calculated (B3LYP/6-31G(d)) structures of (a) the cis transition state derived from compound **4a** and (b) the trans transition state derived from compound **4a**. Carbon atoms are green, oxygen atoms are red, nitrogen atoms are blue, sulfur atoms are yellow, and hydrogen atoms are white.

The surprising reversal in cation stability between citronellal and compound **4a** is intriguing, but can be rationalized readily by examining the structures (Figure 6) of the cations in detail. In the case of both cations derived from citronellal (Figure 6a,b), weak C−H···O interactions exist between a hydrogen atom on one of the two methyl groups and the oxygen atom of the hydroxyl group. By contrast, in the case of the cis cation derived from compound **4a**, this interaction is weaker, as judged by a longer C−H···O and less lengthening of the C−H bond. In the case of the trans cation, this interaction is completely absent—the hydrogen atom lies well outside the sum of the van der Waals radii of the interacting atoms. It is not clear from our calculations why this interaction should be disfavored in the case of trans **4a**. However, it presumably results from the differing juxtapositions of the interacting groups with respect to the highly polar sulfonamide.

Others have invoked the importance of electrostatic interactions in calculations on related systems. Houk has shown through computational modeling that the presence of a heteroatom lone pair on an enophile can have a large effect on the endo/exo

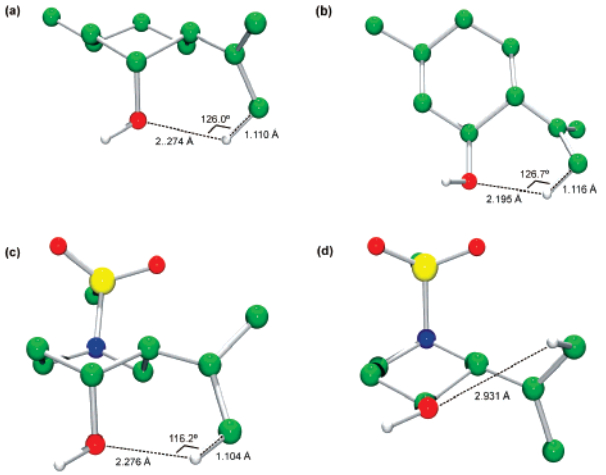


FIGURE 6. C−H···O interactions in the calculated (B3LYP/6-31G-(d)) structures of (a) the cis cation derived from citronellal, (b) the trans cation derived from citronellal, (c) the cis cation derived from compound **4a**, and (d) the trans cation derived from compound **4a**. Some hydrogen atoms are omitted for clarity. Carbon atoms are green, oxygen atoms are red, nitrogen atoms are blue, sulfur atoms are yellow, and hydrogen atoms are white.

stereoselectivity of the ene reaction.[22] By modeling the transition structures of the ene reaction of propene with formaldehyde imine, he was able to show that electrostatic interactions between the nitrogen lone pair and the central carbon atom of propene actually dictate the endo/exo outcome of the reaction. More recently, Mikami has performed similar calculations on the Lewis acid-catalyzed carbonyl ene reaction of *E*-but-2-ene with glyoxylate, showing that there is a similar electrostatic interaction between the oxygen lone pair and the relevant carbon atom of the ene component.[23]

Conclusion

In summary, we have discovered a highly diastereoselective synthesis of cis and trans 3,4-disubstituted piperidines from simple acyclic precursors. Cyclization catalyzed by Brønsted acids or by Lewis acids at low temperature affords predominantly the cis product, which is the kinetic product of the reaction, equilibrating to the thermodynamically more stable trans isomer under Lewis acid catalysis at higher temperatures. DFT calculations at the B3LYP/6-31G(d) level of theory indicate that the cis carbocation that would result from a stepwise cyclization mechanism is more stable than the trans carbocation, possibly as a result of stabilizing overlap between the oxygen lone pair and the empty p-orbital at the carbocationic center. Calculations (B3LYP/6-31G(d)) of the transition states for cyclization via a concerted mechanism also indicate that the cis product should be favored, with the cis transition state being lower in energy than the corresponding trans transition state. The method should find application in the synthesis of more complex molecules, and the switch between kinetic and thermodynamic control with Brønsted and Lewis acid catalysts may be applicable to other carbonyl ene cyclizations.

Experimental Section

Computational Methods Ab initio electronic structure calculations were carried out with GAMESS[24] running on a Linux cluster. The version dated 22 Nov 2004 was used in all calculations. The transition states for the cyclizations of citronellal and compound **4a** were located by generation of an initial guess, using the linear synchronous transit (LST) method and then refinement at the HF/6-31G level of theory within GAMESS. This model transition state was then used to construct an initial guess for the transition state leading to the appropriate cis or trans product. This guess was refined at the B3LYP/6-31G(d) level of theory to a transition state structure possessing a single imaginary vibration that corresponded to the reaction coordinate.

Typical Procedure for the Alkylation: Preparation of *N*-(3-Hydroxypropyl)-4-methyl-*N*-(3-methylbut-2-enyl)benzenesulfonamide. Cesium carbonate (1.85 g, 5.7 mmol) was added to a solution of *N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (1.0 g, 4.4 mmol) in DMF (25 mL). The reaction mixture was stirred at ambient temperature for 30 min before 1-bromo-3-methylbut-2-ene (0.5 mL, 4.4 mmol) was added. The resulting mixture was stirred for a further 90 min and then poured into water. The aqueous phase was then extracted with diethyl ether, and the combined organic phases washed with brine, dried over $MgSO_4$, and evaporated in vacuo to leave a yellow crystalline solid that was purified by flash column chromatography (silica; eluent 2:1 hexane: ethyl acetate) to give *N*-(3-hydroxypropyl)-4-methyl-*N*-(3-methylbut-2-enyl)benzenesulfonamide (1.13 g, 86%) as a white crystalline solid: mp 42−43 °C (from hexane/ethyl acetate); R_f 0.28; IR (Nujol) 3531, 2929, 2875, 1669, 1598, 1337, 1305, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.63 (s, 3H), 1.67−1.74 (m, 2H) 2.33 (t, $J = 7.0$ Hz, 1H), 2.42 (s, 3H), 3.21 (t, $J = 6.5$ Hz, 2H), 3.71−3.76 (m, 2H), 3.80 (d, $J = 7.0$ Hz, 2H), 4.93−4.99 (m, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.68 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 21.5, 25.7, 31.0, 43.7, 45.8, 58.8, 118.9, 127.2, 129.6, 136.95, 136.97, 143.2; MS (CI) *m/z* 315 ($[M + NH_4]^+$, 4%), 298 ($[M + H]^+$, 100), 247 (25), 230 (26), 143 (45). Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71. Found: C, 60.35; H, 8.0; N, 4.8.

Typical PCC Oxidation Procedure: Preparation of 4-Methyl-*N*-(3-methylbut-2-enyl)-*N*-(3-oxopropyl)benzenesulfonamide (4a) Celite (2 g) was added to a suspension of PCC (1.09 g, 5.0 mmol) in CH_2Cl_2 (10 mL). The resultant slurry was stirred vigorously for 5 min before being cooled to 0 °C. A solution of *N*-(3-hydroxypropyl)-4-methyl-*N*-(3-methylbut-2-enyl)benzenesulfonamide (1.0 g, 3.36 mmol) in CH_2Cl_2 (5 mL) was then added in one portion. After the solution was warmed to room temperature and stirred for 2 h, $NaHSO_4$ (3.0 g) and diethyl ether (25 mL) were added and the mixture was stirred vigorously for 15 min before being filtered through silica, washed with diethyl ether, and dried over $MgSO_4$. Concentration of the filtrate in vacuo followed by flash column chromatography (silica; eluent 3:1 petroleum ether:ethyl acetate) gave 4-methyl-*N*-(3-methylbut-2-enyl)-*N*-(3-oxopropyl)benzenesulfonamide (**4a**) (0.67 g, 67%) as a colorless oil: R_f 0.42; IR (thin film) 2924, 2731, 1723, 1674, 1598, 1338, 1305, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.66 (s, 3H), 2.43 (s, 3H), 2.79 (dt, $J = 1.1$, 7.1 Hz, 2H), 3.36 (t, $J = 7.1$ Hz, 2H), 3.76 (d, $J = 7.0$ Hz, 2H), 4.92−5.00 (m, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.70 (d, $J = 8.0$ Hz, 2H), 9.75 (t, $J = 1.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 21.6, 25.8, 41.0, 44.1, 46.5, 118.7, 127.2, 129.8, 136.3, 137.7, 143.5, 200.6; MS (CI) *m/z* 313 ($[M + NH_4]^+$, 100%), 296 ($[M + H]^+$, 22), 275 (5), 245 (70), 227 (11), 189 (4), 142 (64), 112 (7), 98 (7), 80 (8); HRMS (ES) calcd for $C_{15}H_{21}NO_3NaS$, 318.1140 $[M + Na]^+$, found 318.1129 $[M + Na]^+$.

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TPAP Oxidation Procedure: Preparation of 4-Methyl-*N*-(2-ethylidenecyclopentane)-*N*-(3-oxopropyl)benzenesulfonamide (4c). Solid TPAP (5 mol %) was added in one portion to a stirred mixture of *N*-(3-hydroxypropyl)-4-methyl-*N*-(2-ethylidenecyclopentane)-benzenesulfonamide (0.20 g, 0.60 mmol), *N*-methylmorpholine *N*-oxide (0.109 g, 0.90 mmol), and powdered 4 Å molecular sieves (0.50 g) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 75 min and then filtered through silica, eluting with CH_2Cl_2. The residue was dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (silica; eluent 2:3 ethyl acetate:petroleum ether) afforded 4-methyl-*N*-(2-ethylidenecyclopentane)-*N*-(3-oxopropyl)benzenesulfonamide (**4c**) (0.17 g, 85%) as a colorless oil: R_f 0.51; IR (neat) 2947, 2361, 1720, 1450, 1335, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54−1.66 (m, 4H), 2.13−2.15 (m, 2H), 2.16−2.20 (m, 2H), 2.42 (s, 3H), 2.80 (t, J = 7.0 Hz, 2H), 3.37 (t, J = 7.0 Hz, 2H), 3.75 (d, J = 7.4 Hz, 2H), 5.08−5.15 (m, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 25.9, 26.2, 28.8, 33.8, 41.1, 44.0, 48.0, 114.1, 127.3, 129.7, 136.5, 143.3, 149.2, 200.5; MS (ES) *m*/*z* 344 (100%, $[M + Na]^+$).

Typical Procedure for the Ene-Type Cyclization: Preparation of (3*S,4*S**)-3-Isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (7a).** Methyl aluminum dichloride (1 M solution in hexanes, 0.34 mL, 0.34 mmol) was added to a solution of aldehyde **4a** (100 mg, 0.34 mmol) in chloroform (10 mL). The resulting mixture was heated under reflux for 16 h, after which it was quenched by addition of water. The aqueous phase was then extracted with diethyl ether and the combined organic phases washed with brine, dried over $MgSO_4$, and evaporated in vacuo to leave a colorless oil that was purified by flash column chromatography (silica; eluent 2:1 petroleum ether:ethyl acetate) to give first (3*R**,4*S**)-3-isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (**6a**) (6 mg, 6%) as a white crystalline solid, data as below. Further elution afforded (3*S**,4*S**)-3-isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (**7a**) (74 mg, 74%) as a white crystalline solid: mp 149−151 °C (from petroleum ether/ethyl acetate); R_f 0.24; IR (neat) 3391, 2920, 2904, 1647, 1597, 1458, 1334, 1304, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.58−1.68 (m, 1H), 1.71 (s, 3H), 1.85 (br s, 1H), 2.01−2.06 (m, 1H), 2.17−2.27 (m, 2H), 2.37 (dt, J = 2.8, 12.4 Hz, 1H), 2.43 (s, 3H), 3.44 (dt, J = 4.5, 10.1 Hz, 1H), 3.75−3.77 (m, 1H), 3.81−3.86 (m, 1H), 4.89 (s, 1H), 5.01 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.5, 32.5, 45.0, 48.8, 51.6, 69.4, 114.7, 127.6, 129.7, 133.6, 142.4, 143.6; MS (CI) *m*/*z* 296 ($[M + H]^+$, 100%), 278 (4), 247 (5), 189 (5), 143 (10), 124 (8), 79 (4), 69 (10). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 61.0; H, 7.1; N, 4.6.

Typical Procedure for the Prins-Type Cyclization with Concentrated Hydrochloric Acid: Preparation of (3*R,4*S**)-3-Isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (6a).** Concentrated hydrochloric acid (37%, 0.10 mL, 1.02 mmol) was added to a solution of aldehyde **4a** (100 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 16 h, after which it was quenched by addition of water. The aqueous phase was then extracted with diethyl ether and the combined organic phases washed with brine, dried over $MgSO_4$, and evaporated in vacuo to leave a colorless oil that was purified by flash column chromatography (silica; eluent 2:1 petroleum ether: ethyl acetate) to give (3*R**,4*S**)-3-isopropenyl-1-(toluene-4-sulfonyl)-piperidin-4-ol (**6a**) (79 mg, 79%) as a white crystalline solid: mp 89−91 °C (from petroleum ether/ethyl acetate); R_f 0.36; IR (neat) 3519, 2920, 2904, 1651, 1597, 1447, 1323, 1304, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (br s, 1H), 1.77 (s, 3H), 1.81−1.95 (m, 2H), 2.37 (d, J = 12.1 Hz, 1H), 2.42 (s, 3H), 2.55−2.62 (m, 2H), 3.55−3.59 (m, 2H), 3.96 (d, J = 2.2 Hz, 1H), 4.58 (s, 1H), 4.96 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.8, 31.1, 40.5, 43.5, 46.7, 63.0, 112.2, 127.6, 129.6, 133.4, 143.4, 143.8; MS (CI) *m*/*z* 296 ($[M + H]^+$, 100%), 278 (4), 257 (5), 189 (8), 143 (13), 124 (15), 105 (4), 79 (11). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 61.0; H, 7.1; N, 4.6. Further elution afforded (3*S**,4*S**)-3-isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (**7a**) (4 mg, 4%) as a white crystalline solid, data as above.

Typical Procedure for the Prins-Type Cyclization with HCl-Saturated CH_2Cl_2: Preparation of (3*R,4*S**)-3-(1-Benzyl-2-phenylvinyl)-1-(toluene-4-sulfonyl)piperidin-4-ol (6f).** Anhydrous HCl gas was bubbled through a −78 °C solution of **4f** (152 mg, 0.34 mmol) in CH_2Cl_2 for 30 min, followed by stirring at this temperature for a further 6 h. Removal of the solvent in vacuo and purification of the residue by flash column chromatography (silica; eluent 2:1 petroleum ether:ethyl acetate) afforded (3*R**,4*S**)-3-(1-benzyl-2-phenylvinyl)-1-(toluene-4-sulfonyl)piperidin-4-ol (**6f**) (108 mg, 71%) as a white crystalline solid: mp 129−130 °C; R_f 0.38; IR ($CDCl_3$) 3438, 3026, 1644, 1493, 1338, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62−1.72 (m, 1H), 1.74−1.86 (m, 1H), 2.48 (s, 3H), 2.55 (dt, J = 2.9, 11.4 Hz, 1H), 2.67 (t, J = 11.4 Hz, 1H), 3.19−3.24 (m, 1H), 3.29−3.38 (m, 1H,), 3.47−3.54 (m, 1H), 3.62 (s, 2H), 4.00 (s, 1H), 6.46 (s, 1H), 7.22 (d, J = 7.0 Hz, 2H), 7.27−7.32 (m, 6H), 7.33−7.44 (m, 4H), 7.45 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 32.8, 40.2, 41.8, 42.5, 44.6, 67.7, 126.5, 126.8, 127.6, 128.4, 128.5, 128.7, 128.9, 129.6, 132.1, 133.0, 137.4 139.6, 140.4, 143.3; MS (ES) *m*/*z* 470 (100%, $[M + Na]^+$). Anal. Calcd for $C_{27}H_{29}NO_3S$: C, 72.45; H, 6.53; N, 3.13. Found: C, 72.5; H, 6.6; N, 2.9.

Typical Procedure for the Prins-Type Cyclization−Elimination with HCl-Saturated CH_2Cl_2 Followed by Ammonia: Preparation of (3*R,4*S**)-3-Cyclohex-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-ol (6d).** Anhydrous HCl gas was bubbled through a −78 °C solution of **4d** (50 mg, 1.48 mmol) in CH_2Cl_2 for 30 min, followed by stirring at this temperature for a further 2 h. The solvent was removed in vacuo and the residue dissolved in THF (10 mL). Concentrated aqueous ammonia was added (10 mL) and the mixture was stirred for 18 h. Following removal of the THF in vacuo the aqueous phase was extracted with CH_2Cl_2 and the combined organic phases washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Purification of the residue by flash column chromatography (silica; eluent 2:1 petroleum ether:ethyl acetate) afforded (3*R**,4*S**)-3-cyclohex-1-enyl-1-(toluene-4-sulfonyl)piperidin-4-ol (**6d**) (35 mg, 70%) as a white crystalline solid: mp 94−95 °C (from petroleum ether/ethyl acetate); R_f 0.62; IR ($CDCl_3$) 2910, 2360, 1670, 1590, 1334, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48−1.65 (m, 4H), 1.82−2.06 (m, 5H), 2.25−2.30 (m, 1H), 2.43 (s, 3H), 2.51−2.61 (m, 2H), 3.50−3.60 (m, 2H), 3.91−3.93 (m, 1H), 5.31 (s, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 22.3, 22.8, 25.2, 28.6, 31.0, 40.6, 43.4, 46.9, 63.2, 123.6, 127.6, 129.7, 133.5, 136.2, 143.4; MS (ES) *m*/*z* 358 ($[M + Na]^+$, 100%). Anal. Calcd for $C_{18}H_{25}NO_3S$: C, 64.45; H, 7.51; N, 4.18. Found: C, 64.5; H, 7.8; N, 4.0.

Typical Procedure for Removal of the *p*-Toluenesulfonyl Group: Preparation of (3*R,4*S**)-3-Cyclohept-1-enylpiperidin-4-ol (22e).** To a solution of **6e** (62 mg, 0.18 mmol) in THF (0.8 mL) at −78 °C was added sodium naphthalenide (0.8 mL of 1 M solution in THF). After 5 min the reaction was quenched by the addition of MeOH (0.3 mL) and then allowed to warm to ambient temperature. The reaction mixture was then diluted with H_2O and acidified to pH 1 with 3 M HCl. The aqueous layer was washed with Et_2O, basified to pH 9 with 3 M NaOH, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield (3*R**,4*S**)-3-cyclohept-1-enylpiperidin-4-ol (**22e**) (25 mg, 71%) as a colorless oil: IR (thin film) 3020, 2925, 1522, 1216, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29−1.43 (m, 2H), 1.44−1.60 (m, 2H), 1.62−1.80 (m, 2H), 1.86−1.95 (m, 1H), 2.03−2.29 (m, 5H), 2.68−3.03 (m, 5H), 4.00 (br s, 1H), 5.50 (t, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3, 29.5, 30.6, 34.3, 34.9, 35.8, 42.5, 45.9,

51.9, 65.9, 130.5, 146.5; MS (ES) *m*/*z* 196 (100%, $[M + Na]^+$); HRMS (ES) calcd for $C_{12}H_{22}NONa$, 196.1701 $[M + Na]^+$, found 196.1694 $[M + Na]^+$.

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Supporting Information Available: Experimental procedures for all compounds not detailed in Experimental Section and ^1H and ^{13}C NMR spectra for all compounds; CIF files and ORTEP plots for all crystal structures reported; coordinate files for the calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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