A Novel Tandem Michael Addition/Meerwein−Ponndorf−Verley Reduction: Asymmetric Reduction of Acyclic α,β-Unsaturated Ketones Using A Chiral Mercapto Alcohol

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Abstract: The introduction of a thiol group into a chiral alcohol reagent for asymmetric Meerwein−Ponndorf−Verley (MPV) reductions allows asymmetric reduction of α,β-unsaturated ketones to secondary alcohols and allylic alcohols via a novel tandem Michael addition/MPV reduction. The reaction of acyclic α,β-unsaturated ketones **1** and an optically active 1,3-mercapto alcohol (−)-**2** using dimethylaluminum chloride afforded the MPV reduction products **3** diastereoselectively in very high yields (up to 96%). Mechanistic studies elucidated (1) the structure of the chelation complex **D** with (−)-**2** and Me_2AlCl, (2) an asymmetric 1,7-hydride shift (intramolecular MPV reduction), and (3) dynamic kinetic resolution via reversible Michael addition. Subsequent reductive desulfurization of the MPV products **3** with a modified Raney nickel system led to the highly enantioselective reduction of α,β-unsaturated ketones to saturated secondary alcohols in 96−98% ee. β-Elimination of the corresponding sulfoxides gave the allylic alcohols in 86−98% ee. Applications to the asymmetric reduction of a synthetic intermediate **1m** of prostaglandins and to a new asymmetric synthesis of the (+)-Rove beetle pheromone **11** are described.

Introduction

The Meerwein−Ponndorf−Verley (MPV) reduction, discovered in the 1920s, still is a useful method for the reduction of carbonyl compounds because of its chemoselectivity.[1] Various alkoxides of Li,[2] Mg,[3] and early transition metals (Sc,[4] Y,[4] lanthanide,[5] Zr,[6] Hf,[6] Ta[7]), variants of the original aluminum isopropoxide, have been used in this reaction. In the 1950s and 1960s, asymmetric versions of the *intermolecular* MPV reduction of ketones employing optically active alcohols as chiral sources were widely studied. However, only low or moderate enantioselectivity was realized by this methodology.[8] Conversely, it was shown that *intramolecular* MPV reduction (1,5-hydride shift) proceeds with extremely high stereoselectivity,[9] though this method is not applicable to asymmetric reduction of the usual ketones without a chiral alcohol moiety. Evans and co-workers devised a catalytic highly enantioselective MPV reduction using a chiral samarium catalyst.[10] Noyori and co-workers also exploited an excellent asymmetric transfer hydrogenation of aromatic ketones using a late transition metal chiral ruthenium or iridium catalyst. The reaction is similar to the MPV

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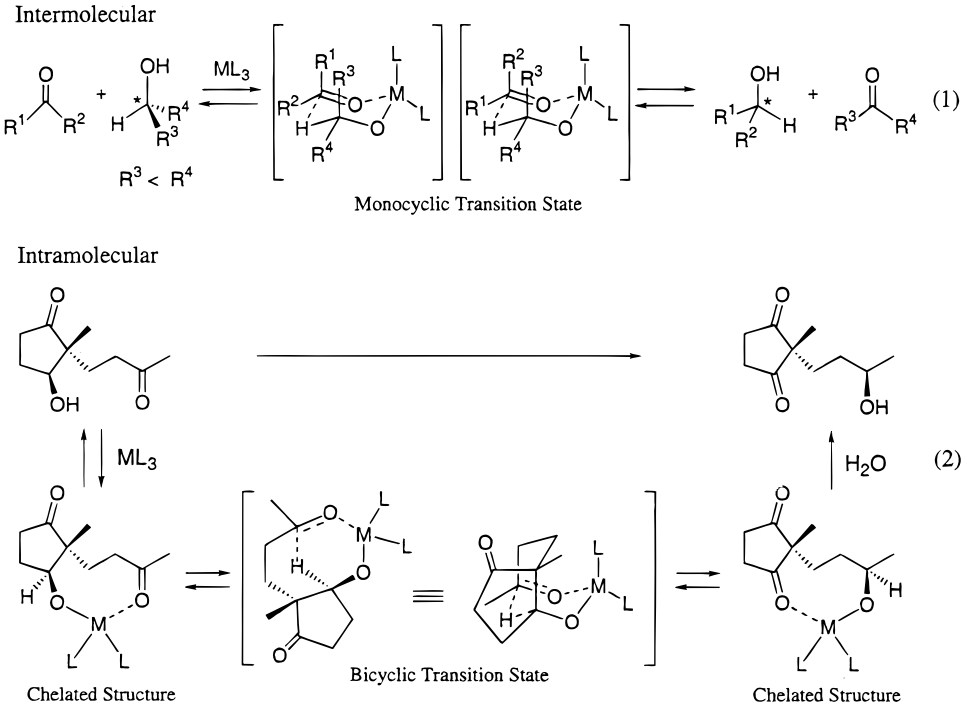
Scheme 1. Inter- and Intramolecular Meerwein−Ponndorf−Verley Reductions



reduction but has a different mechanism.[11] These reactions are limited in that only aryl methyl ketones give products in excellent enantiomeric excesses. Therefore, we decided to investigate a new type of asymmetric MPV reduction that would have few substrate limitations. We report herein the full account of the asymmetric reduction[12] of α,β-unsaturated ketones to saturated secondary alcohols or allylic alcohols, using an optically active mercapto alcohol as a chiral reagent via *a novel tandem Michael addition/MPV reduction* and subsequent desulfurization.

Results and Discussion

A. Design of a Novel Asymmetric Tandem Michael Addition/MPV Reduction. We began by analyzing the transition states of various inter- and intramolecular asymmetric MPV reductions (eqs 1 and 2, Scheme 1). The low enantioselectivity in eq 1[8] can be attributed to a relatively small energy difference between the two possible six-membered monocyclic transition states, in which the controlling factor of the enantiofacial selectivity of the carbonyl group is the bulkiness of the four substituents. In eq 2,[9a] the high enantioselectivity presumably is due to the formation of the single bicyclic transition state by steric restriction of the chiral alcohol moiety on the eight-membered chelated structure. Although intramolecular MPV reduction is superior to intermolecular reduction in terms of stereoselectivity, the former has two serious drawbacks: (1) another asymmetric synthesis is required in the substrate preparation and (2) the ketone moiety remains in the product, making its removal difficult.

To overcome these disadvantages, we designed a tandem Michael addition/MPV reduction of an α,β-unsaturated ketone **1** using Lewis acid and a chiral 1,3-mercapto alcohol **2** (Scheme 2). Michael addition of **2** to **1** using Lewis acid proceeded easily to give the sulfide **A** containing ketone and chiral alcohol moieties, which then underwent intramolecular MPV reduction (*1,7-hydride shift*) to give the MPV product **B** with high stereoselectivity. Removal of the ketone moiety from **3** by desulfurization afforded the optically active saturated alcohol **4** or the allylic alcohol **5**.

Since the intramolecular MPV conversion of **A** to **B** is reversible, a large energy difference favoring **B** over **A** is needed to provide the driving force for the reaction. Generally, a large energy change is not expected in an intramolecular MPV reduction because the substrate and the product usually have the same kind of functional groups. The contribution of the structural change of the reagent (mercapto alcohol) to the driving force of the reaction biased **A** into **B** also must be considered. The torsional strain of a cyclopentanol system, including its eclipsing interactions, is partially released by conversion to the ketone. The strain energy difference in a five-membered ring would be greater than that in a six-membered ring or an acyclic system.

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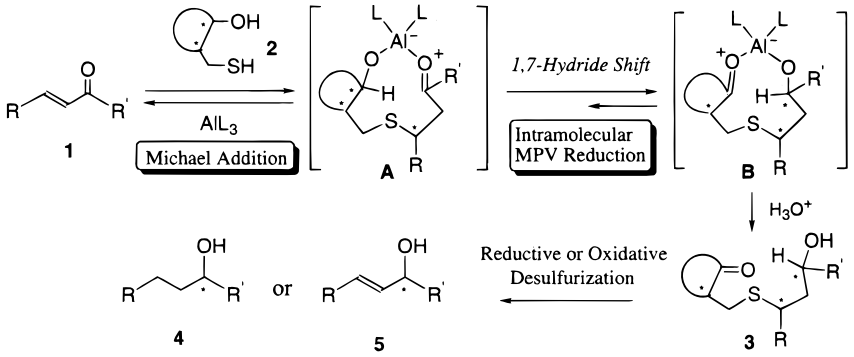
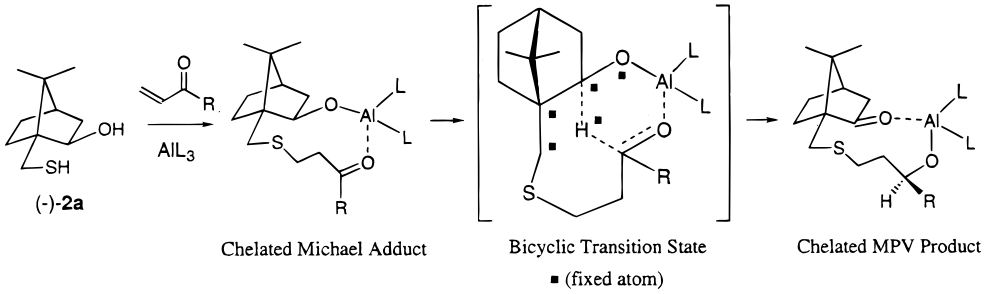
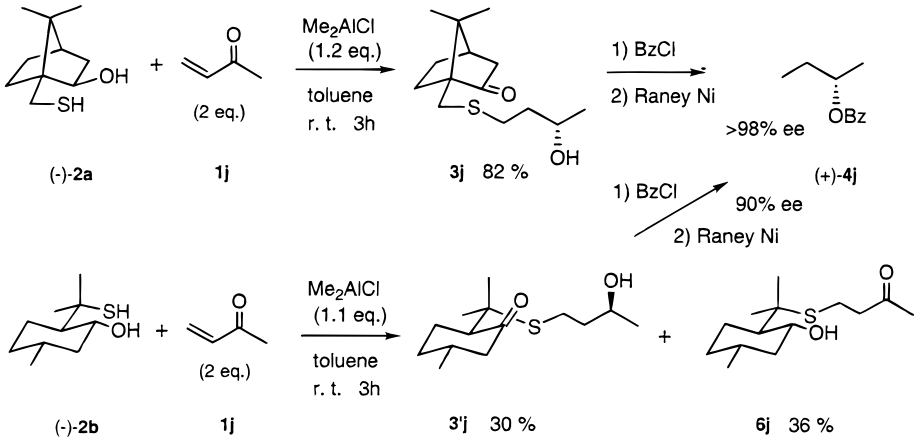
Scheme 2. Asymmetric Reduction of α,β-Unsaturated Ketones via Tandem Michael Addition−MPV Reduction



Scheme 3. Aluminum Complexes of Michael Adduct and MPV Product of (−)-**2a**



Scheme 4. Comparison of Chiral Mercapto Alcohols **2a**,**b** for Tandem Michael−MPV Reduction



Using the above criteria, we chose 10-mercaptoisoborneol [(+)- or (−)-**2a**][13] as a chiral reagent and an acyclic α,β-unsaturated ketone as the substrate for this asymmetric reduction. In the MPV reduction of the Michael adduct from (−)-**2a** and an α,β-unsaturated ketone, a single bicyclic transition state is expected due to the five fixed atoms of the 10-mercaptoisoborneol (**2a**) moiety in the normally flexible 10-membered-ring chelated structure (Scheme 3), thus making possible a high yield and high diastereoselectivity.

To confirm the above hypothesis, we compared the reactions of methyl vinyl ketone (**1j**) with mercapto alcohols **2a**[13] and **2b**[14] using Me_2AlCl in toluene at room temperature for 3 h (Scheme 4). The reaction of **2a** afforded only the MPV product **3j**. On the other hand, **2b** gave both the Michael adduct **6j** (36%) and the MPV product **3′j** (30%). Benzoylation of **3j** and **3′j** and desulfurization with Raney nickel gave the corresponding benzoate **4j** in >98% ee and 90% ee, respectively (determination of optical purity will be described later). As expected, the five-membered-ring alcohol **2a** was notably superior to the six-membered-ring alcohol **2b**. The intermolecular MPV reduction of ketones **7** and **8** with borneol (**2c**) and isoborneol (**2d**) (same method) gave the secondary alcohols **4a** (6% ee) and **4f** (47% ee), respectively (Scheme 5), thus confirming the superiority of the intramolecular process.

B. Optimization of Reaction Conditions (Solvents, Lewis Acids, Temperatures, Times). Reaction conditions were optimized using benzalacetone (**1a**) and (−)-**2a** (98% ee). The optical purity of 4-phenyl-2-butanol (**4a**) obtained by reductive desulfurization[15] of **3a** was determined by chiral HPLC analysis (Daicel CHIRALCEL OD). Assignment of the stereochemistry on the chiral carbon attached to a sulfur atom in **3a** will be discussed later. Dichloromethane was the solvent providing **4a** with the highest (97%) ee. Other solvents giving **4a** in >90%

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Scheme 5. Intermolecular MPV Reduction Using Borneol and Isoborneol

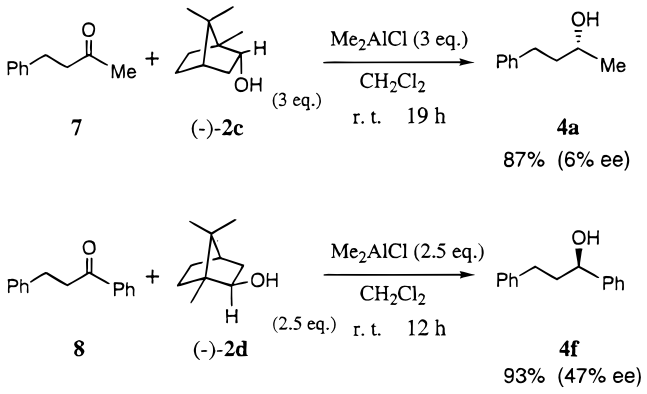
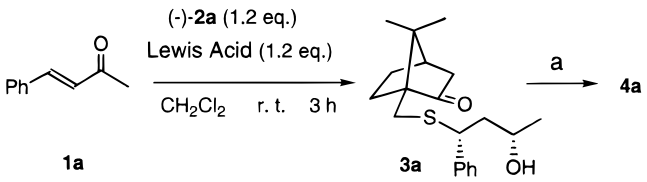


Table 1. Reaction Data



entry	Lewis acid	yield (%) of **3a**	% ee[b] of **4a**
1	Me_2AlCl	61	97
2	Et_2AlCl	66	95
3	Pr_2AlCl	35	90
4	$EtAlCl_2$	n.r.[c]	
5	$AlCl_3$	n.r.[c]	

[a] Reductive desulfurization with Raney Ni−$NaPH_2O_2$. [b] Determined by HPLC Chiralcel OD. [c] Chiral mercapto alcohol **2a** was decomposed.

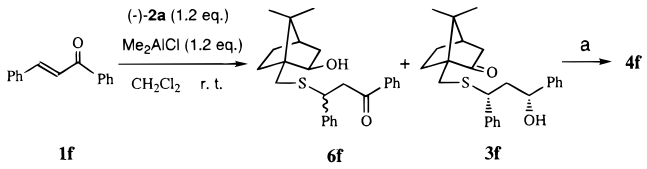
ee were benzene, toluene, and Et_2O. The yield of **3a** was highest in hexane, but the product ee was somewhat lower than that in dichloromethane. The reaction did not occur in THF presumably due to its high coordinating ability to the aluminum Lewis acid.

Dialkylaluminum chlorides proved to be the most successful Lewis acid for this reaction (Table 1). Among the organoaluminums tested, Me_2AlCl clearly was the best with regard to the ee of the MPV product. Higher alkyl substituents than methyl on aluminum decreased ee. $EtAlCl_2$ and $AlCl_3$ caused decomposition of **2a** due to their stronger Lewis acidity.

The temperature effect was next studied. The MPV reduction did not occur at −78 °C, it proceeded at 0 °C, but the yield was higher at room temperature (ca. 20 °C). Higher temperatures (ca. 35 °C) caused the decomposition of **2a** with Me_2AlCl. The ee values of **4a** at 0 °C and at room temperature were equal and very high (97%), indicating that stereoselectivity of the attack on the carbonyl group is independent of temperature, probably due to the rigid bicyclic transition state (Scheme 3).

We initially assumed that prolonged reaction time decreased product ee, because the MPV reduction is known to be reversible. Therefore, the above reactions were quenched at relatively short times (3 h). The moderate yields of the products **3** and isolation of the adducts **6** prompted us to examine the relationship of reaction times and yields as well as ee values of **4**. Results using *trans*-chalcone (**1f**) are summarized in Table 2. The ratio of the Michael adduct **6f** to the MPV product **3f** decreased as reaction time was prolonged. After 24 h, the ratio reached a plateau (1:>20) with corresponding enhancement of the yield to 85%, in contrast to 59% after 3 h. The most important observation was that the ee of **4f** derived from **3f** remained constant irrespective of reaction time. This strongly

Table 2. Relationship of Reaction Time and Optical Purity



reaction time (h)	**6f**[b]:**3f**	yield (%) of **3f**	ee (%) of **4f**
1.5	1:2.1		96
3	1:2.3	59	96
6	1:3.6		96
12	1:13.1		96
24	1:>20	85	96
48	1:>20		96

[a] Reductive desulfurization with Raney Ni−$NaPH_2O_2$. [b] Diastereomeric mixture (ca. 1:1).

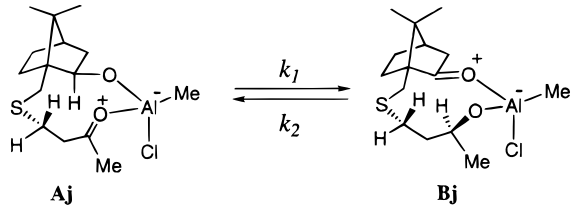


Figure 1. Aluminum complexes of Michael adduct and MPV product.

suggests that the MPV reduction proceeds via an *asymmetric intramolecular 1,7-hydride shift* in which a rigid bicyclic transition state is involved.

C. MOPAC PM3 Calculations. PM3 calculations (MOPAC version 6) were performed to clarify the energy difference between the Michael adduct and the MPV product. To simplify calculations, we used Michael adduct **Aj** and MPV product **Bj** of **2a** with methyl vinyl ketone (**1a**). The calculated heats of formation were −172.14 kcal/mol for **Aj** and −173.96 kcal/mol for **Bj**, indicating the latter to be 1.82 kcal/mol more stable than the former.

The ratio of the two components in equilibrium is related to their free energy difference. If the MPV reduction is *an intramolecular reaction* (proved later), Figure 1, the entropy can be neglected in the free energy equation. The free energy then can be approximated by the enthalpy. The equilibrium constant ($K = k_1/k_2$) can be calculated to be 22.8. This constant is close to the experimental value (>20) for 24 and 48 h. Thus, it may be concluded that the reaction reaches equilibrium after 24 h.

D. Asymmetric Reduction of α,β-Unsaturated Ketones to Secondary Alcohols. Using the above optimization results, we set about generalizing the reaction. Reductions of various α,β-unsaturated ketones **1a**−**h**, bearing an aromatic group as R^1, are summarized in Table 3. Reaction products **3a**−**h** were reductively desulfurized using the Raney nickel−$NaPH_2O_2$ combination system[15] to give the corresponding products **4a**−**h** in high yields. No racemization of the optically active secondary alcohol was observed.[16] Reaction of benzalacetone (**1a**) with **2a** (1.2 equiv, 98% ee) and Me_2AlCl (1.2 equiv) (room temperature, 12 h) in CH_2Cl_2 under N_2 gave **3a** in 83% yield. Reductive desulfurization of **3a** resulted in (*S*)-4-phenyl-2-butanol (**4a**) with 97% ee in 89% yield (entry 1, Table 3). The yield of **3a** was improved to 94% by using benzene instead of

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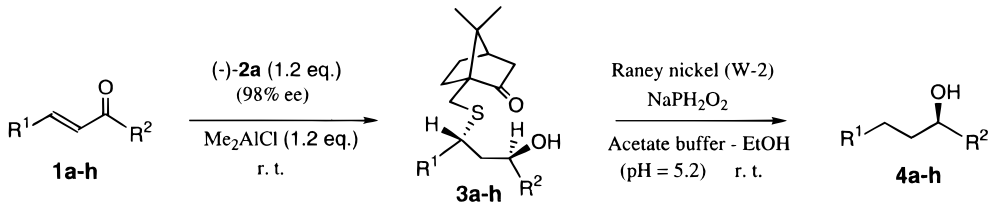
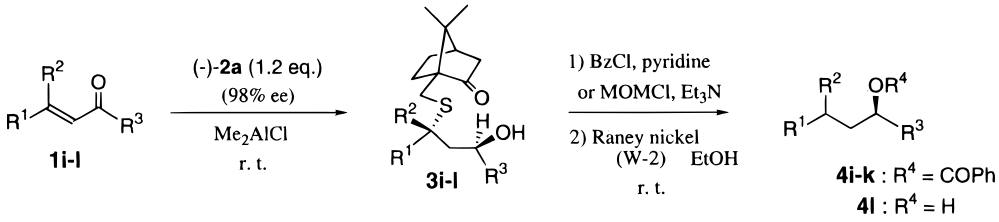
Table 3. Tandem Michale−MPV Reaction and Subsequent Reductive Desulfurization



	tandem Michael−MPV reaction						reductive desulfurization			
entry	compd	R^1	R^2	solv.	time (h)	yield (%)[a] of **3**	time (min)	yield (%)[a] of **4**	% ee[b] of **4**	config.
1	**1a**	Ph	Me	CH_2Cl_2	12	83	40	89	97	*S*[c]
2	**1a**			benzene	12	94	40	88	89	*S*
3	**1b**	Ph	Et	CH_2Cl_2	13	90	20	91	98	*S*
4	**1c**	Ph	Pr	CH_2Cl_2	16	81	20	95	98	*S*
5	**1d**	Ph	Bu	CH_2Cl_2	12	83	40	89	97	*S*
6	**1e**	Ph	Oct	CH_2Cl_2	12	90	40	99	98	*S*
7	**1f**	Ph	Ph	CH_2Cl_2	25	89	20	96	96	*R*
8	**1f**			benzene	24	94	20	99	95	*R*
9	**1g**	*p*-MeOPh	Ph	CH_2Cl_2	33	75	20	97	96[d]	*R*[e]
10	**1g**			benzene	38	88	20	85	92[d]	*R*
11	**1h**	*p*-Tolyl	Ph	CH_2Cl_2	16	73	20	90	98	*R*[e]

[a] Isolated yield. [b] HPLC analysis using a Daicel Chiralcel OD column unless otherwise noted. [c] Determined by X-ray crystallographic analysis of the corresponding sulfone **10** of **3a**. [d] Daicel Chiralpak AS. [e] Determined by the CD spectrum comparison with **4f**.

Table 4. Tandem Michael−MPV Reaction and Subsequent Reductive Desulfurization



	tandem Michael−MPV reaction							reductive desulfurization			
entry	compd	R^1	R^2	R^3	solv.	time (h)	yield (%)[a] of **3**	time (h)	yield (%)[b] of **4**	% ee[c] of **4**	config.
1	**1i**	Me	Me	Me	CH_2Cl_2	16	90	1.5	75	98	*S*[d]
2	**1i**				benzene	15	96	4	73	98	*S*[d]
3	**1j**	H	H	Me	CH_2Cl_2	12	82	2[e]	73	98	*S*[d]
4	**1k**	H	H	Pent	CH_2Cl_2	15	82	31	77	97[f]	*R*
5	**1l**	Me	H	Ph	CH_2Cl_2	24	95	24	86[g]	93	*R*

[a] Isolated yield. [b] Overall yield of protection and desulfurization. [c] HPLC analysis using a Daicel Chiralcel OB column unless otherwise noted. [d] Determined by modified Mosher's method: see ref 17. [e] Reflux 2 h. [f] Daicel Chiralcel OF. [g] The MOM group was removed during isolation by SiO_2 chromatography.

CH_2Cl_2 as a solvent, but the ee of **4a** dropped to 89% (entry 2, Table 3). We observed the same phenomenon in the reactions of **1g** and **1f** (entries 7−10, Table 3). Reductions of other α,β-unsaturated ketones, with either an aromatic or an aliphatic substituent as R^2, afforded fairly high yields (73−94%). The ee values of the resulting secondary alcohols were also excellent (96−98%), except for the reaction in benzene (entries 3−11, Table 3).

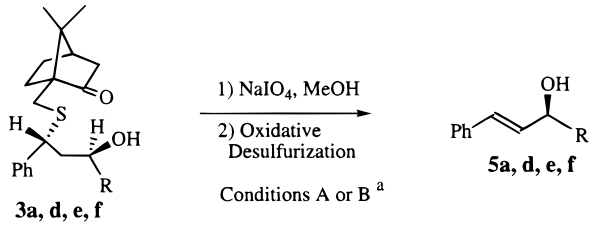
The reaction of α,β-unsaturated ketones **1i**−**l** bearing an aliphatic group as R^1 and R^2, under conditions similar to those in Table 3, proceeded smoothly to give the products **3i**−**l** in high yields (82−96%) (Table 4). With aliphatic α,β-unsaturated ketones, the reductive desulfurization with the Raney nickel combination system[15] did not take place. Therefore, Raney nickel (W-2) was used, after benzoylation of **3** to prevent racemization.[15] In the reductive desulfurization with Raney nickel, the benzoates of **3i**−**k** afforded the corresponding benzoates **4i**−**k** in excellent ee values (97−98%), although the yield was moderate (73−77%). In the reaction of mesityl oxide **1i**, benzene produces a higher yield than in CH_2Cl_2, without lowering the ee (entry 2, Table 4). Since the benzoylation of **3l** bearing a phenyl group as R^3 did not proceed cleanly, the reductive desulfurization of **3l** with Raney nickel was conducted after methoxymethylation of the alcohol.

The conversion of **3** to allylic alcohol **5** is summarized in Table 5. The oxidation of sulfides **3a**,**d**,**e**,**f** with sodium periodate afforded the corresponding sulfoxides in almost quantitative yields. The subsequent β-elimination (toluene reflux) of the sulfoxide of **3a** furnished **5a** quantitatively, but the ee of **5a** was 5% lower than that in the reductive desulfurization (entry 1, Table 5). With a butyl or octyl substituent as R, the allylic alcohols **5d,e** showed excellent ee values (entries 2 and 3, Table 5). However, in the β-elimination of the sulfoxide of **3f**, the ee of **5f** was 86% (entry 4, Table 5). When the β-elimination was conducted at benzene reflux to give **5f** in 72% yield, the ee improved to 91% despite the longer reaction time (entry 5, Table 5). A similar decrease in ee values of optically active alcohols has been reported.[18]

(17) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(18) Barrett, A. G. M.; Kamimura, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1754−1755.

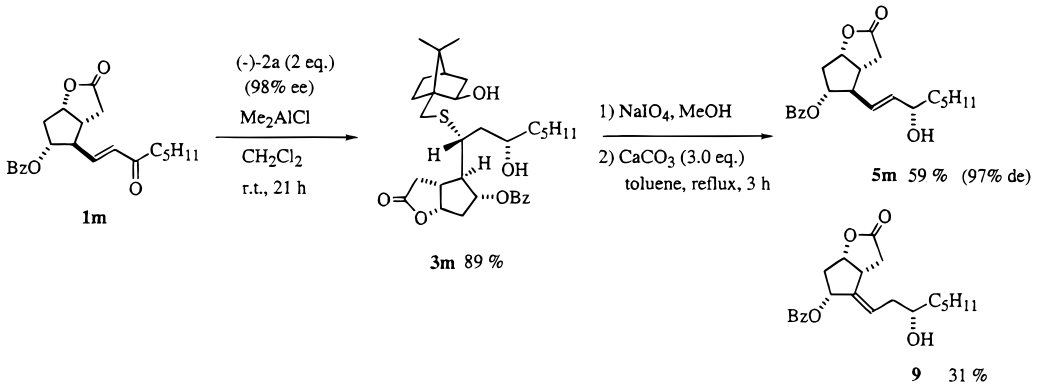
Table 5. Asymmetric Synthesis of Allylic Alcohols



	substrate			oxidation to sulfoxide		oxidative desulfurization				
entry	compd	R	o.p.[b] (%)	time (h)	yield[c] (%)	conditions	time (h)	yield[c] (%)	% ee[d]	config.
1	**3a**	Me	96	22	98	A	4	100	92	*S*
2	**3d**	Bu	98	24	98	A	2	93	98	*S*
3	**3e**	Oct	96	16	100	A	4	95	95	*S*
4	**3f**	Ph	96	20	95	A	4	87	86	*R*
5	**3f**					B	72	72	91	*R*

[a] Method A: $CaCO_3$, 130 °C in toluene.; Method B: $CaCO_3$, 100 °C in benzene. [b] Optical purity of the side chain of **3** which was observed by the reductive desulfurization. [c] Isolated yield. [d] HPLC analysis. See Experimental Section (Supporting Information).

Scheme 6. Asymmetric Reduction of a Synthetic Intermediate of Prostaglandins



Since the substituent on the carbon attached to the sulfur atom in the above substrates **3** is limited to a phenyl group, the elimination of the sulfoxides gives the *E*-allylic alcohol selectively. However, substrates bearing an alkyl group instead of a phenyl group could give both allylic and homoallylic alcohols. To study the reactivity of such a substrate, we tried the asymmetric reduction of the key intermediate in a synthesis of prostaglandins (Scheme 6). Reaction of the optically active **1m** and (−)-**2a** (2 equiv) with Me_2AlCl (2 equiv) after 21 h afforded the sulfide **3m** as a single diastereomer in 89% yield. Oxidation of **3m** and subsequent β-elimination resulted in a 59% yield of allylic alcohol **5m** (97% de) and a 31% yield of homoallylic alcohol **9**. Thus the regioselectivity of the β-elimination appears to be directly proportional to the number of hydrogen atoms on the β- and β'-carbon atoms.

E. Mechanistic Aspects. 1. Structure of the Aluminum Complex of the Chiral Reagent (−)-2a. Two possible structures **C** and **D** were considered for the complex of (−)-**2a** and Me_2AlCl (Scheme 7). Structure **C** was eliminated because the formation of methane gas[19] was observed in the following reactions: (1) the addition of Me_2AlCl into the CH_2Cl_2 solution of (−)-**2a** and (2) the addition of *s*-BuOH into the CH_2Cl_2 solution of Me_2AlCl at room temperature, but not in the reaction of EtSH with Me_2AlCl. Furthermore, methane gas was released from the reaction mixture when 1 equiv of *s*-BuOH was added to the aluminum complex generated from (−)-**2a** and Me_2AlCl. If the aluminum complex of (−)-**2a** had been structure **C**, the tandem reaction of **1f** would have given the deuterated Michael product and/or the deuterated MPV product by quenching the aluminum enolate **E** with 20% DCl. But no deuterium was incorporated into the α position in the products **3f** and **6f**; the structure of the chiral aluminum Lewis acid therefore should be **D**.

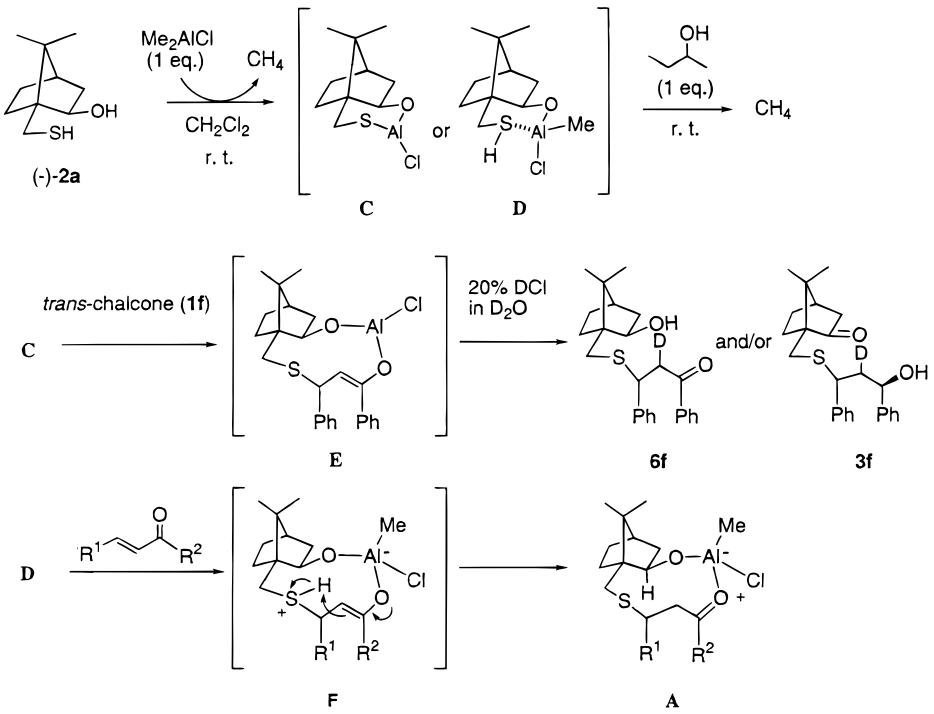
The thiol proton in structure **D** could play an important role in promoting the subsequent MPV reduction. Intermediate **A**, which becomes a substrate for the subsequent MPV reduction, could be produced by proton migration in the aluminum enolate **F** formed by the Michael addition of the complex **D**.

2. Asymmetric Intramolecular 1,7-Hydride Shift.[20] A crossover experiment using Michael adducts revealed this MPV reaction to be *completely an intramolecular hydride shift* (Scheme 8). Thus, a mixture of equimolar amounts of deuterium-labeled Michael adduct **6j(D)** (≈98% D) and the unlabeled Michael adduct **6n** was treated with Me_2AlCl (2.0 equiv) in CH_2Cl_2 at room temperature for 22 h to give the MPV products, labeled **3j(D)** (92%) and unlabeled **3n** (91%), respectively. The deuterium content of all products was measured by integration of their ^1H NMR spectra. The possibility of an intermolecular MPV reaction between the Michael adduct and (−)-**2a** was ruled out by another crossover experiment in which a mixture of equimolar amounts of the deuterium-labeled adduct **6j(D)** (≈98% D) and unlabeled (−)-**2a** was treated with Me_2AlCl (2.0

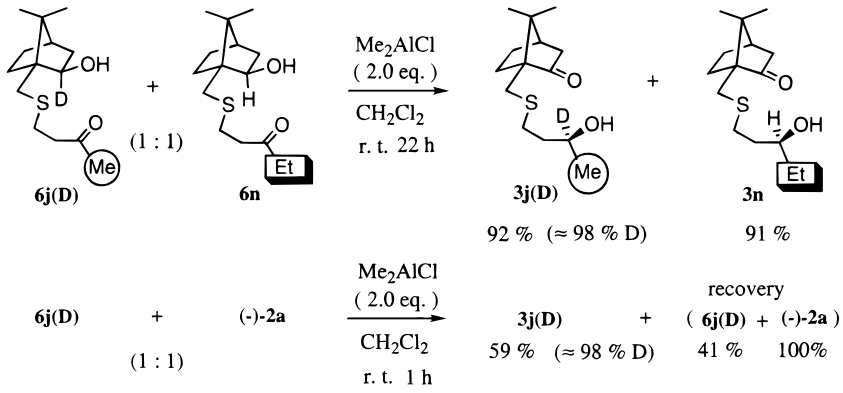
(19) (a) Starowieyski, K. B.; Pasynkiewicz, S.; Skowroñska-Ptasiñska, M. *J. Organomet. Chem.* **1975**, *90*, C43−C44. (b) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573−4576. (c) Ooi, T.; Maruoka, K. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 200−211.

(20) [1,7] sigmatropic rearrangement of conjugated trienes: for example: (a) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1988**, *110*, 8223−8228. (b) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1987**, *109*, 8051−8056.

Scheme 7. Plausible Structures of the Complex from Me_2AlCl and (−)-10-Mercaptoisoborneol (−)-**2a**]



Scheme 8. Crossover Experiments for Intramolecular MPV Reduction (Asymmetric 1,7-Hydride Shift)

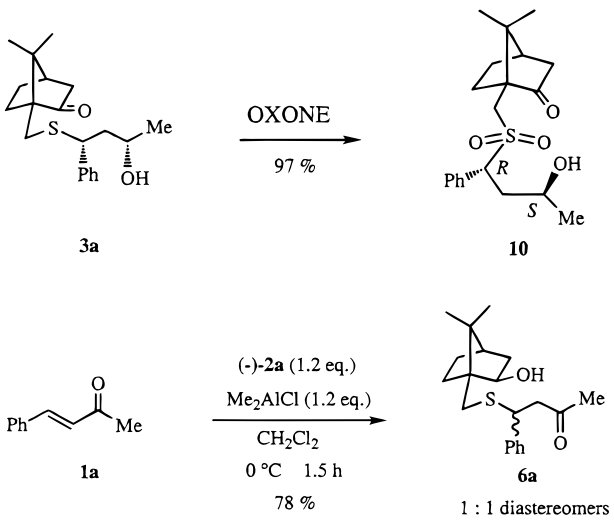


equiv) to give the MPV products **3j(D)** (59%) and recoveries of **6j(D)** (41%) and (−)-**2a** (100%). Although some deuterium dispersion (less than 2%) was observed among the experiments that were repeated several times, almost all the deuterium of **6j(D)** had been retained in the product **3j(D)**. We will discuss this deuterium dispersion below. The crossover experiments showed that this novel MPV reduction indeed proceeded via *an intramolecular 1,7-hydride shift.*

3. Equilibration in the Tandem Michael/MPV Reaction. As shown in Scheme 9, the oily **3a** obtained by the tandem reaction of benzalacetone (**1a**) with (−)-**2a** was converted into crystalline sulfone **10** (97%) by oxidation with OXONE. The chiral carbon attached to the sulfur atom in **3a** was revealed to have the *R*-configuration by X-ray crystallographic analysis of **10**. The reaction of **1a** and (−)-**2a** with Me_2AlCl at 0 °C gave adduct **6a** (78%) as a 1:1 diastereomeric mixture. Subsequent MPV reduction of this 1:1 mixture furnished a single diastereomer of **3a** in which the configuration of both chiral centers was highly controlled.

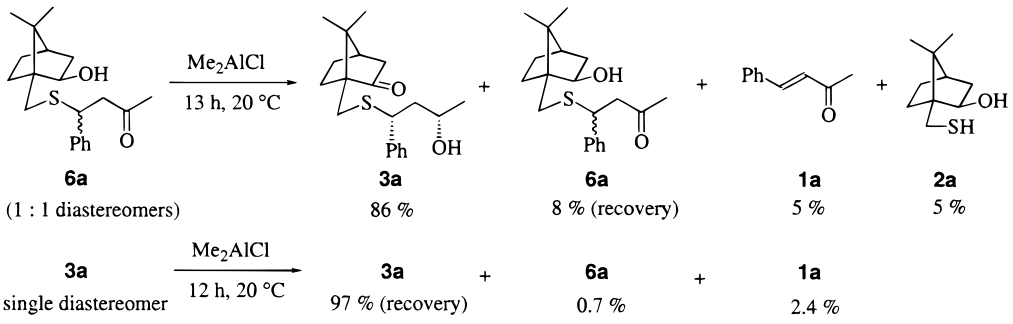
These facts suggested that this tandem Michael addition/MPV reduction involves a dynamic kinetic resolution[21] when the reversibly formed Michael adduct bears a β-substituent. To confirm the involvement of this equilibrium/resolution, the 1:1

Scheme 9

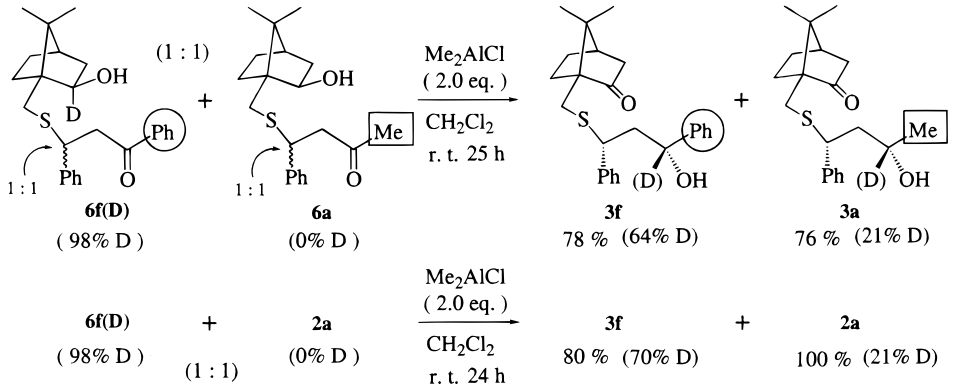


mixture of **6a** diastereomers was subjected to MPV reduction with Me_2AlCl (1.2 equiv, in CH_2Cl_2, 20 °C, 13 h; Scheme 10). Single diastereomer **3a** (86%) was obtained along with the

Scheme 10. Equilibrium in a Tandem Michael Addition−MPV Reduction



Scheme 11. Crossover Experiments between Michael Adducts **6a** and **6f(D)**



recovered ketone adduct (8%, 1:1 diastereomers), benzalacetone (**1a**) (5%), and (−)-**2a** (5%). The MPV product **3a** was subjected to similar reaction conditions. Only a trace of the Michael adduct (0.7%) and benzalacetone (**1a**) (2.4%) was produced; 97% of the starting material was recovered. Since these reactions afforded both the retro-Michael and the retro-MPV products, the two reactions were confirmed to be reversible (equilibrium). Appreciable formation of **1a** and **6a** in the reaction of **3a** suggests that the reversible MPV reaction step might be kinetically controlled to a considerable extent at about 20 °C.

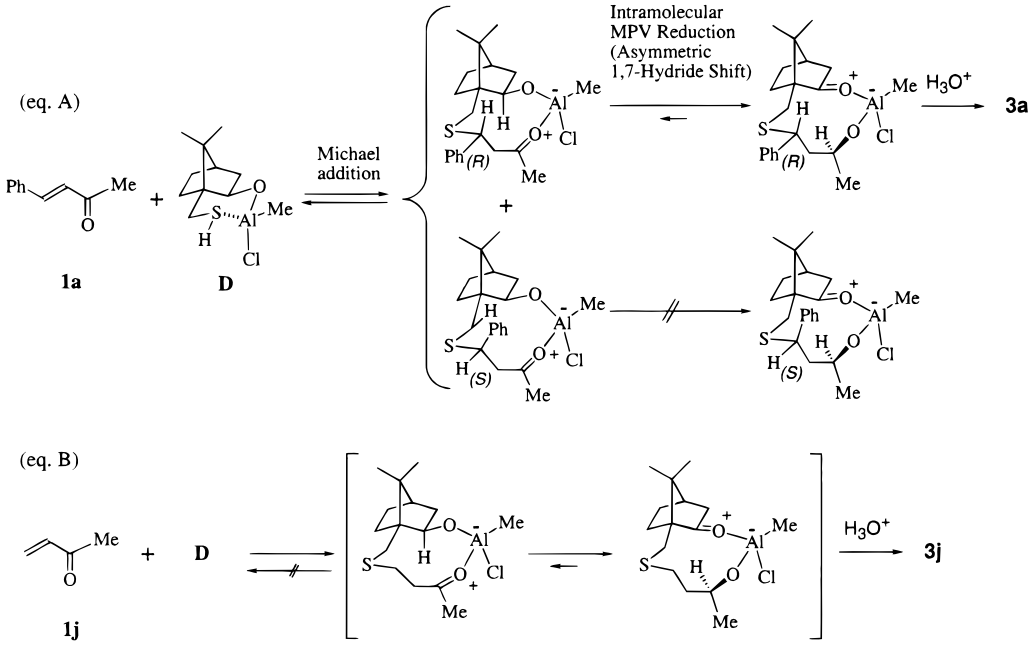
Consequently, crossover experiments were conducted to verify the equilibrium between the Michael adduct and the α,β-unsaturated ketone (Scheme 11). A mixture (1:1) of deuterated **6f(D)** and unlabeled **6a** was subjected to MPV reduction with Me_2AlCl at 20 °C for 24 h to give partially deuterated **3f** (64% incorporation of D) and **3a** (21% incorporation of D). The reaction using deuterated **6f(D)** and unlabeled alcohol **2a** gave partially deuterated **3f** (70% D) and **2a** (21% D). This MPV reduction is not an intermolecular reaction but an intramolecular reaction, according to the experiments in Scheme 8. The above results indicate that during the MPV reduction, the Michael adducts exist in equilibrium between the retro-Michael reaction and the Michael addition. The observed deuterium dispersion could be explained by the partial formation of deuterium-labeled **6a** and unlabeled **6f** via this equilibrium. Although the experiments in Schemes 8 and 11 seem to be in conflict with the deuterium dispersion, it is believed that these experiments are fundamentally consistent with the observation of trace amounts of deuterium dispersion in Scheme 8, i.e., the retro-Michael reactions of **6j** and **6n** in Scheme 8 are retarded by kinetic control near room temperature. The difference in the above crossover experiments is whether the α,β-unsaturated ketone generated from a Michael adduct has a substituent (phenyl group) at the β-position and whether these structural changes cause significant differences in the rate of the retro-Michael reaction.

A summary of a plausible mechanism for the tandem Michael addition/MPV reduction is illustrated by eqs A and B in Scheme 12. The β-substituted α,β-unsaturated ketone **1a** reacts reversibly with the chiral aluminum complex **D** derived from (−)-**2** and Me_2AlCl to give two diastereomeric chelated adducts. The *R*-diastereomer (at the carbon attached to the sulfur atom) is subjected to the reversible intramolecular MPV reduction, even though the reduction does not proceed by complete thermodynamic control. Based on PM3 calculations, the distance from the migrating hydrogen to the carbonyl carbon in the chelated *R*-diastereomer is about 3.1−3.4 Å. Therefore, the *R*-diastereomer of the 10-membered ring could easily proceed to the rigid bicyclic transition state. On the other hand, the phenyl ring in the *S*-diastereomer lies on the β-face of the 10-membered chelate ring, which places it very near a C-10 hydrogen of the isoborneol skeleton. Therefore, MPV reduction in the *S*-diastereomer is greatly retarded by its high transition state energy. Consequently, the production of a single isomer **3a** is attributable to dynamic kinetic resolution[21] via reversible Michael addition and kinetically controlled intramolecular MPV reduction of one of the two Michael adducts (eq A). The tandem reaction of the nonsubstituted α,β-unsaturated ketone **1j** consists of the nearly irreversible Michael addition by kinetic control and the reversible intramolecular MPV reduction by thermodynamic control (eq B).

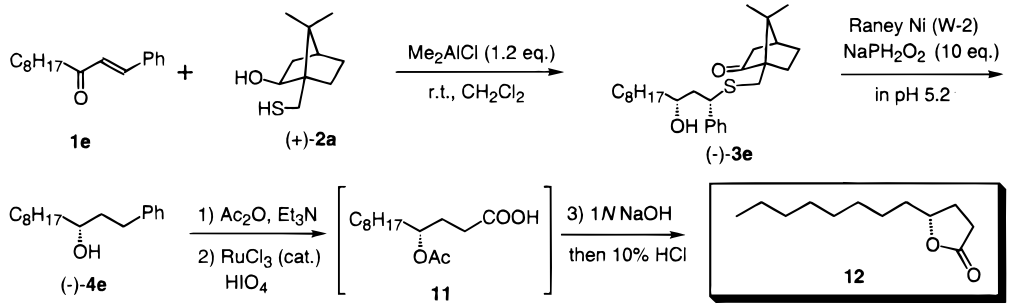
F. Application to Asymmetric Synthesis of the Rove Beetle Pheromone. The Rove beetle pheromone (+)-**12** is an optically active γ-lactone, the synthesis of which would demonstrate this tandem Michael addition/MPV reduction. Representative asymmetric syntheses[22] of the Rove beetle pheromone include asymmetric reduction of α,β-alkynyl ketones with BINAL-H,[22a] asymmetric reduction of γ-keto esters with BINAP-Ru(II) catalysts,[22b] and asymmetric ene reaction of aldehydes.[22c] Our

(21) (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56. (b) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475−1490,and references therein.

Scheme 12. A Plausible Mechanism for a Novel Tandem Michale Addition−MPV Reduction



Scheme 13. Asymmetric Synthesis of the (+)-Rove Beetle Pheromone



synthetic route to the (+)-Rove beetle pheromone is illustrated in Scheme 13. The tandem Michael addition/MPV reduction of (*E*)-1-phenyl-1-undecen-3-one (**1e**) with (+)-**2a** (97% ee) gave the MPV product in 90% yield. Subsequent reductive desulfurization with Raney Ni−$NaPH_2O_2$ afforded (*R*)-(−)-1-phenylundecan-3-ol (**4e**) in 99% yield and 97% ee. Ruthenium oxide oxidation[23] of (−)-**4e** after acetylation gave (*R*)-4-acetoxydodecanoic acid (**11**), which was hydrolyzed with 1 N sodium hydroxide and acidified with 10% hydrochloric acid to afford the (*R*)-(+)-Rove beetle pheromone **12** in 75% yield from (*R*)-1-phenylundecan-3-ol (**1e**). The specific rotation {$[\alpha]^{18}_D$ +37.3 (0.82, MeOH), lit.[22c] $[\alpha]^{26}_D$ +36.6 (0.29, MeOH) (>98% ee)} and spectroscopic data of the synthetic **12** were identical with those reported in the literature. The overall yield of this synthesis was 67% (5 steps).

Conclusion

Introduction of a thiol group as a tether to connect a secondary alcohol with acyclic α,β-unsaturated ketones allows for a new type of MPV reduction, i.e., a *tandem Michael addition/MPV reduction*, making it possible to circumvent the low enantioselectivity of the classical asymmetric *intermolecular* MPV reduction.

In this novel MPV reduction, we observed for the first time both *an asymmetric 1,7-hydride shift* and a *dynamic kinetic resolution via a reversible Michael addition*. High diastereoselectivity was achieved at the two newly generated chiral carbons bearing the alcohol and the sulfide. The facial selectivity of the oxycarbenium ion on the 10-membered ring chelated structure **A** reached 98−100% in dichloromethane, based on the optical purity (98% ee) of the chiral alcohol used. The high facial selectivity at the carbonyl carbon atom is due to the formation of a rigid bicyclic transition state (because of the five fixed atoms in the bornane skeleton) even though the usual 10-membered ring is supposed to be conformationally flexible. Highly enantioselective reduction of acyclic α,β-unsaturated ketones to saturated secondary alcohols or to their benzoates (96−98% ee) and allylic alcohols (91−98% ee) was achieved by subsequent reductive or oxidative desulfurization. Because of its effectiveness in reducing both aromatic and aliphatic α,β-unsaturated ketones, this reaction should be eminently suitable for a wide range of substrates.

We have also synthesized the (+)-Rove beetle pheromone in high enantiomeric purity and high overall yield in only a few synthetic steps.

(22) (a) Noyori, R.; Tomino, M.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717−6725. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509−5512. (c) Masuya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1994**, *35*, 7965−7968. (d) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169. (e) Vigneron, J. P.; Bloy, V. *Tetrahedron Lett.* **1980**, *21*, 1735. (f) Sugai, T.; Mori, K. *Agric. Biol. Chem.* **1984**, *48*, 2497−2500.

(23) Carlsen, P. H. J.; Katuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

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Supporting Information Available: Experimental details and table of results, including crystallographic data, atomic coordinates, anisotropic displacement parameters, bond lengths and angles, torsion angles, and nonbonded contacts (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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