$MgSO_4$, and concentrated in vacuo. The crude product was recrystallized from ether/hexane to give **13** in 86% yield.

13: mp 117-118 °C; IR (KBr) 1585, 1495, 1450, 1305, 1150, 1090, 750, 720, 700 cm^{-1}; ^1H NMR δ 7.97-7.14 (m, 15 H), 4.72 (s, 2 H), 3.60 (dd, J = 14.3, 1.8 Hz, 1 H), 3.34 (dd, J = 14.3, 7.9 Hz, 1 H), 2.85 (dd, J = 7.9, 1.8 Hz, 1 H), 2.52 (m, 1 H), 2.20 (m, 1 H), 1.87-1.42 (m, 7 H), 1.14 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ 140.7, 136.7, 135.7, 133.3, 129.1, 128.4, 128.3, 128.2, 127.8, 127.1, 126.4, 112.5, 85.6, 85.4, 54.7, 47.8, 39.0, 31.4, 30.1, 25.3, 20.2, 19.5. Anal. Calcd for $C_{29}H_{22}O_4S$: C, 73.08; H, 6.77. Found: C, 72.88; H, 6.99.

General Procedure for Ozonolysis of 9b, 7a, and 10b and Esterification. A solution of the 2-methylene ketone (0.9 mmol) in ethyl acetate (50 mL) was cooled to -78 °C. A stream of ozone was bubbled through the solution until it was blue. The blue solution was warmed to rt, and nitrogen gas was bubbled through the mixture to expel surplus ozone. After concentration of the mixture in vacuo, the residue was dissolved in acetic acid (12 mL), and one drop of concd H_2SO_4 and 35% H_2O_2 (1.5 mL) were added. The mixture was stirred at 25 °C overnight and subjected to reduced distillation (50 °C (10 mm Hg)) to remove considerable amounts of acetic acid and water. The residue was dissolved in methanol (2 mL), and PTSA dihydrate (4 mg) was added. After being stirred at 25 °C for 2 h, methanol was removed in vacuo and the residue was dissolved in ether (30 mL). The ether solution was washed with water (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate).

14:[16] $[\alpha]^{25}_D$ +11.0° (c 1.00, $CHCl_3$) [lit. S-form: $[\alpha]^{20}_D$ +14.6 (neat)]; IR (neat) 1740, 1260, 1200, 1170 cm^{-1}; ^1H NMR δ 3.69 (s, 3 H), 3.67 (s, 3 H), 2.37-2.29 (m, 3 H), 1.94-1.82 (m, 2 H), 1.68-1.51 (m, 2 H), 0.90 (t, J = 7.3 Hz, 3 H).

16:[17] $[\alpha]^{25}_D$ +12.7° (c 1.20, EtOH) [lit. S-form: $[\alpha]^{23}_D$ +13.5 (c 1.48, EtOH)]; IR (neat) 1740, 1250, 1200, 1175 cm^{-1}; ^1H NMR δ 3.68 (s, 3 H), 3.67 (s, 3 H), 2.50-2.40 (m, 1 H), 2.35-2.29 (m, 2 H), 1.70-1.57 (m, 3 H), 1.52-1.40 (m, 1 H), 1.16 (d, J = 7.0 Hz, 3 H).

18:[18] $[\alpha]^{25}_D$ -39.4° (c 1.03, $CHCl_3$) [lit. R-form: $[\alpha]^{22}_D$ +103.5 (neat)]; IR (neat) 1740, 1600, 1495, 735, 700 cm^{-1}; ^1H NMR δ 7.31-7.27 (m, 5 H), 3.73 (q, J = 7.0 Hz, 1 H), 3.65 (s, 3 H), 1.50 (d, J = 7.0 Hz, 3 H).

Stereoselective Synthesis of Cis 2,3-Disubstituted Cycloheptanones by Kinetic Protonation

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The hitherto unknown stereochemistry concerning the formation of 2,3-disubstituted cycloheptanones by the Michael addition reaction was studied. The Michael addition of thiophenol to 3-substituted 2-methylenecycloheptanones in the presence of triethylamine in THF at ambient temperature produced 3-substituted 2-[(phenylthio)methyl]cycloheptanones with high cis selectivity (>96/4), which was unequivocally established by ^1H NMR and X-rays analyses. An isomerization experiment and theoretical calculations (AM1) suggest that the origin of the observed high stereoselectivity can be explained in terms of kinetic protonation of the corresponding enolate intermediate.

Introduction

The kinetic protonation of enolates is a useful technique for producing stereoisomers (diastereomers) with high stereoselectivity in synthetic organic chemistry.[1] The formation of the kinetic product has been well interpreted in terms of the concept of the least hindered approach of a proton donor to the enolates which usually leads to the thermodynamically less stable stereoisomers.[1] Thus, the deprotonation-kinetic protonation sequence is often used to obtain the less stable stereoisomer from its more stable counterpart via epimerization.[2]

The Michael addition of nucleophiles to substituted α,β-unsaturated carbonyl compounds and their analogues involves a protonation process of the resulting enolates and hence raises an issue of diastereoselectivity.[3-6] The resulting stereochemistry generally depends on the protonation conditions; protonation at low temperatures leads to the kinetic product, while the product of thermodynamic control is formed at higher temperatures. Recently, there have been several reports dealing with the stereochemistry of protonation of 2,3-disubstituted endocyclic enolates formed by the Michael addition of carbanions to 2-substituted 2-cyclopentenones and 2-cyclohexenones.[5,6] It was found that highly stereoselective protonation of 2,3-disubstituted cyclohexanone enolates was achieved under kinetic conditions to give cis products,[5,6] and the predom-

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(1) For reviews, see: (a) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263. (b) Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J.-C. *Bull. Soc. Chem. Fr.* **1984**, 421.

(2) (a) Zimmerman, H. E.; Nevins, T. E. *J. Am. Chem. Soc.* **1957**, *79*, 6559. (b) Seebach, D. Beck, A. K.; Lehr, F.; Weller, T.; Colvin, E. W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 397. (c) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733. (d) Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 5567. (e) Takano, S.; Yamada, S.; Numata, H.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1983**, 760. (f) Reference 4a.

(3) For the conjugate addition of organocopper reagents to acyclic enones with kinetic protonation, see: (a) Yamamoto, Y., Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1984**, 904. (b) Fleming, I.; Lewis, J. J. *J. Chem. Soc., Chem. Commun.* **1985**, 149. (c) Yamamoto, Y.; Yamada, J.-I.; Uyehara, T. *J. Am. Chem. Soc.* **1987**, *109*, 5820.

(4) For the conjugate addition of heteroatom nucleophiles with kinetic protonation, see: (a) Kamimura, A.; Sasatani, H.; Hashimoto, T.; Kawai, T.; Hori, K.; Ono, N. J. *Org. Chem.* **1990**, *55*, 2437. (b) Hori, K.; Higuchi, S.; Kamimura, A. *J. Org. Chem.* **1990**, *55*, 5900. (c) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 6556.

(5) (a) Liotta, D.; Saindane, M.; Barnum, C.; Zima, G. *Tetrahedron* **1985**, *41*, 4881. (d) Hatzigrigoriou, E.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* **1985**, *41*, 5045.

(6) (a) Luchetti, J.; Krief, A. *Tetrahedron Lett.* **1981**, *22*, 1623. (b) Roux-Schmitt, M. C.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* **1981**, *37*, 1927.

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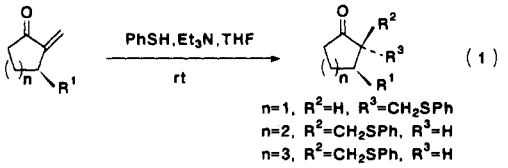
inant formation of cis 2,3-disubstituted cyclopentanones were observed by careful selection of kinetic protonation conditions.[5] Base- or acid-catalyzed epimerization of these alkanones easily occurred to produce the trans isomers.

3-Substituted 2-[(phenylthio)methyl]cyclopentanones and -heptanones were derived from the corresponding optically active 3-substituted 2-methylenecycloalkanones by the Michael addition of thiophenol as a means to determine the enantiomeric purity of the enones (eq 1).[7] It

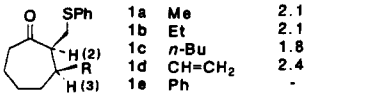


(1)

was found that cis 2,3-disubstituted cycloheptanones were formed with high stereoselectivity (>96/4) even under mild conditions where trans 2,3-disubstituted cyclopentanones were produced from the analogous five-membered enones. Thus, the decision was made to study the hitherto unexplored stereochemistry of 2,3-disubstituted cycloheptanones[8] through an isomerization (epimerization) experiment, ^{1}H NMR and X-ray analyses, and molecular orbital (MO) calculations, to seek the origin of the observed high stereoselectivity. Our experimental results together with the outcome of our theoretical calculations are described herein.

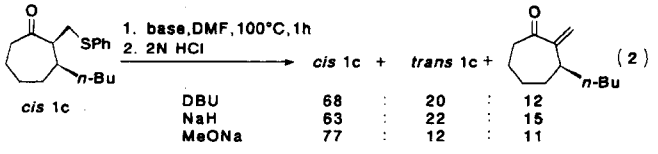
Results and Discussion

Optically active 3-substituted-2-methylenecycloheptanones[7] were exposed to thiophenol in the presence of 5 mol % triethylamine in THF at ambient temperature for 2–3 h (eq 1). A single stereoisomer was obtained in every case in a 60–65% yield with high stereoselectivity (>96/4). The cis stereochemistry was tentatively assigned to the products **1a–1e** on the basis of the vicinal coupling constants between H(2) and H(3) and the base-catalyzed isomerization experiment described below. The observed $J_{H(2)-H(3)}$ (1.8–2.4 Hz for **1a–1d**) were consistent with a



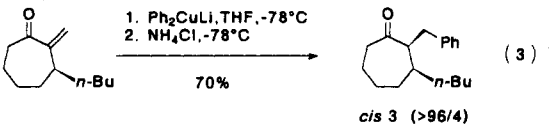
	R	$J_{H(2)-H(3)}$ (Hz)
1a	Me	2.1
1b	Et	2.1
1c	*n*-Bu	1.8
1d	CH=CH$_2$	2.4
1e	Ph	-

probable chairlike form with one alkyl substituent in a pseudoaxial position and the other one in a pseudoequatorial position. Treatment of **1c** with 10 mol % of bases such as DBU, NaH, and MeONa in DMF at 100 °C for 1 h resulted in partial isomerization to produce a mixture of stereoisomers along with the formation of the 2-methylene ketone (eq 2). Et_3N was totally ineffective,



(2)

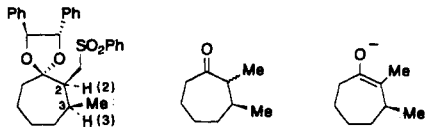
implying that the above PhSH/Et_3N system offered kinetic reaction conditions.[9,10] It was also found that 3-butyl-2-methylenecyclohexanone underwent conjugate addition of PhSH in the presence of Et_3N in THF at room temperature. This transformation provided *cis*-3-butyl-2-[(phenylthio)methyl]cyclohexanone (**2**) with high stereoselectivity (>96/4)) (eq 1), which was isomerized to give a cis/trans (50/28) mixture upon treatment with DBU in DMF for 1 h at 100 °C. Further, it was observed that through the conjugate addition of lithium diphenylcuprate (Ph_2CuLi) to 3-butyl-2-methylenecycloheptanone in THF at −78 °C, followed by probable kinetic protonation at the same temperature, 3-butyl-2-benzylcycloheptanone (**3**) with a small $J_{H(2)-H(3)}$ (1.8 Hz) was obtained with high stereoselectivity (>96/4) (eq 3). These results suggest that



(3)

the cis stereoisomer should be a product of kinetic control. The $J_{H(2)-H(3)}$ of **1e** was hard to extract because of its very complicated coupling pattern. Nevertheless, it was also assumed that **1e** has the same cis geometry since base-catalyzed isomerization occurred to give a mixture of stereoisomers.

To confirm the presumed cis geometry (and to find the absolute configuration of **1a–1e**[7]), we performed an X-ray analysis of one of the optically active products. In order to obtain a single crystal, the product **1a** was converted to acetal **4** by acetalization with (*S,S*)-(−)-hydrobenzoin and oxidation with *m*-CPBA.[7] As expected, an X-ray analysis of **4** showed that the seven-membered ring took on a stable chairlike conformation and the two alkyl substituents unequivocally assumed a cis relation.[11] The vicinal coupling constant $J_{H(2)-H(3)}$ of **4** was definitely less than 1.8 Hz, although it was impossible to read the exact value, indicating that the dihedral angle (71.6°) between H(2)–C(2)–C(3)–H(3) was very close to that of **1a**. Therefore, it is presumed that **1a** should also take a chairlike conformation with the cis geometry of the alkyl substituents.



4 5 6

It has not been established to date which stereoisomer of the 2,3-disubstituted cycloheptanones is thermodynamically more stable, or is the kinetic product of the corresponding enolate intermediate in protonation.[8] From the above experimental results, it was predicted that the cis stereoisomer was the product of the kinetic protonation of the enolate ion and that there is not a great difference in the thermodynamic stability of the two stereoisomers, since the base-catalyzed isomerization experiment produced a mixture of the stereoisomers as shown in eq 2.

In order to verify our assumption, we carried out molecular orbital calculations using the AM1 method.[12,13] *cis-*

(7) See the previous paper in this issue.

(8) The structure of clavularin A and B, certain cis and trans 2,3-disubstituted cyclopent-6-en-1-ones, was elucidated by ^{1}H NMR studies and their total synthesis; see: (a) Endo, M.; Nakagawa, M.; Hamamoto, Y.; Nakanishi, T. *J. Chem. Soc., Chem. Commun.* **1983**, 322 and 980. (b) Urecht, R. *J. Chem. Soc., Chem. Commun.* **1984**, 989. (c) Still, W. J.; Shi, Y. *Tetrahedron Lett.* **1897**, *28*, 2489.

(9) Very recently, the conjugate addition of thiols to acyclic α,β-unsaturated carboxylic acid derivatives involving an analogous kinetic protonation process has been reported; see ref 4c.

(10) Protonation at the α-carbon of ketone enolates has been reported to be a quite fast process in protic media; see: Chiang, Y.; Kresge, J.; Santaballa, J. A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 5506.

(11) The ORTEP drawing of **4** is included in the supplementary material.

(12) Stewart, J. J. P. MOPAC Ver. 5, JCPE P014.

(13) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

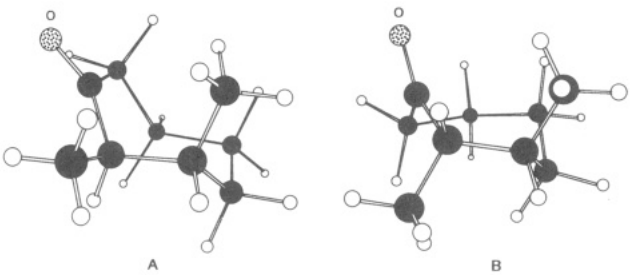


Figure 1. Optimized structures of the most stable conformations of *cis*- and *trans*-**5** using the AM1 method.

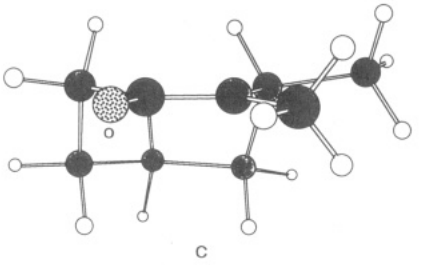


Figure 2. Optimized structure of the most stable conformation of enolate ion **6** using the AM1 method.

and *trans*-2,3-dimethylcycloheptanones **5** were chosen as the model molecules in order to examine the possibility of thermodynamic control of the stereochemistry. There were many candidates for stable conformations because of the flexibility of the seven-membered ring. We executed the optimization for more than 18 possible conformations for each isomer. The optimized structures of the most stable conformations for *cis*-**5** (conformer **A**) and *trans*-**5** (conformer **B**) are shown in Figure 1. Conformer **A** adopts a chairlike structure, in which the two methyl groups are located in the pseudoaxial and the pseudoequatorial positions, while *trans*-**5** preferred the somewhat twisted chairlike conformer **B**, in which the two methyl groups are located in the pseudoaxial positions. The total energies of these conformations were calculated to be −1694.385 eV for **A** and −1694.453 eV for **B**, i.e., *trans*-**5** is more stable by 1.6 kcal/mol than *cis*-**5**. This result means that *trans*-**5** should be preferentially formed at room temperature if the stereochemistry of **5** is thermodynamically governed. This conclusion is inconsistent with the actual, stereoselective formation of *cis*-**5** as described above.

The most favorable conformation of the enolate derivative of **5** was then calculated to evaluate the stereochemical course of the protonation. We optimized a number of possible conformations of the enolate ion **6**. The most stable conformation of **6**, conformer **C**, has a chairlike seven-membered-ring structure as shown in Figure 2. The dihedral angle between the two methyl groups is estimated to be 8.2°. In the protonation process, a proton should approach from the top side of the ring to give *cis*-**5** selectively, since the seven-membered-ring skeleton prohibits a proton from approaching from the bottom side due to steric reasons as can be easily judged from the structure of conformer **C**. Hence, it is concluded that under kinetic conditions, protonation of the enolate ion **6** will predominantly produce the cis isomer. Thus, our calculations are consistent with the experimental results described above, showing that the observed high stereoselectivity is attributed to the kinetically controlled protonation of the enolate ion.

Conclusions

The Michael addition of nucleophiles such as thiophenol and lithium diphenylcuprate to 3-substituted 2-methylenecyclohexanones provided cis 2,3-disubstituted cycloheptanones with high stereoselectivity (>96/4). The observed cis selectivity was accounted for in terms of the kinetic protonation of the 2,3-disubstituted cycloheptanone enolate intermediate. The MO calculations were well correlated with our experimental results.

Experimental Section

Infrared spectra were recorded as liquid films on NaCl plates. NMR spectra were obtained in $CDCl_3$ solution containing TMS standard. THF and DMF were distilled from sodium benzophenone ketyl and CaH_2, respectively.

General Procedure for Preparation of Cis 3-Substituted 2-[(Phenylthio)methyl]cycloheptanones 1a–1e and *cis*-3-Butyl-2-[(phenylthio)methyl]cyclohexanone (2). To the 2-methylene ketone[7] (1.0 mmol) in THF (5.0 mL) was added a solution of thiophenol (1.5 mmol) and triethylamine (0.05 mmol) at 25 °C. The reaction mixture was stirred for 2–3 h and poured into water (30 mL). The aqueous mixture was extracted with ether (3 × 30 mL). The ether extract was washed with water (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (9:1 hexane–ethyl acetate). See the previous paper in this issue for spectral data of **1a–1e**.

cis-**2**: IR (neat) 1715, 1585, 1480, 740, 695 cm^{-1}; ^1H NMR δ 7.40–7.14 (m, 5 H), 3.26 (dd, J = 13.2, 7.2 Hz, 1 H), 3.12 (dd, J = 13.2, 4.3 Hz, 1 H), 2.50–2.40 (m, 2 H), 2.29 (m, 1 H), 2.07–1.89 (m, 2 H), 1.85–1.60 (m, 2 H), 1.56–1.40 (m, 2 H), 1.34–1.12 (m, 5 H), 0.88 (t, J = 6.7 Hz, 3 H). Anal. Calcd for $C_{17}H_{24}OS$: C, 73.86; H, 8.75. Found: C, 73.56; H, 9.03.

Preparation of *cis*-3-Butyl-2-benzylcycloheptanone (3). To the 3-butyl-2-methylenecycloheptanone[7] (1.0 mmol) in THF (5 mL) was added a precooled (−78 °C) solution of Ph_2CuLi (1.5 mmol) in THF (10 mL) at −78 °C via a stainless cannula. The reaction mixture was stirred for 30 min at −78 °C, and saturated aqueous NH_4Cl solution (30 mL) was added. The aqueous mixture was extracted with ether (3 × 30 mL). The ether extract was washed with water (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20:1 hexane/ethyl acetate).

***cis*-3**: IR (neat) 1700, 1605, 1500, 700 cm^{-1}; ^1H NMR δ 7.25–7.06 (m, 5 H), 3.08 (ddd, J = 9.8, 6.4, 1.8 Hz, 1 H), 3.05 (dd, J = 16.2, 6.4 Hz, 1 H), 2.51 (dd, J = 16.2, 9.8 Hz, 1 H), 2.41 (m, 1 H), 2.23 (m, 1 H), 1.87–1.11 (m, 13 H), 0.82 (t, J = 7.3 Hz, 3 H). Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.35; H, 10.41.

General Procedure for Base-Catalyzed Isomerization. A mixture of the ketone (1.0 mmol) and the base (0.1 mmol) in DMF (5 mL) was heated at 100 °C for 1 h and cooled. To the DMF solution was added 2 N HCl (30 mL). The aqueous mixture was extracted with ether (3 × 30 mL). The ether extract was washed with brine (3 × 30 mL), 2 N HCl (30 mL), and water (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The cis/trans ratio was determined by ^1H NMR analysis of the crude material.

***trans*-1c**: ^1H NMR δ 3.26 (dd, J = 12.8, 3.9 Hz, 1 H) and 3.07 (dd, J = 12.8, 9.7 Hz, ^1H) for CH_2S.

***trans*-2**: ^1H NMR δ 3.32 (dd, J = 13.4, 7.2 Hz, 1 H) and 2.91 (dd, J = 13.4, 7.9 Hz, 1 H) for CH_2S, 2.77 (ddd, J = 4.6, 7.2, 7.9 Hz, 1 H) for H(2).

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Supplementary Material Available: X-ray crystallographic data for compound **4** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.