(from NaH) and **3** in THF at 23 °C for 1 h (84% yield); (2) reduction of lactone–ester to lactol–alcohol using 3.3 equiv of diisobutylaluminum hydride in toluene at −78 °C for 40 min (99%); (3) oxidation to **9** using Collins reagent $[CrO_3(py)_2]$ in methylene chloride at 0 °C for 20 min (85% yield). The enal **9** was treated with allenylborane **10**, generated by reaction (−95 °C, THF) of the lithio derivative of propargyl chloride with triethylborane,[12] and after a reaction time of 1.5 h at −78 °C, the product was isolated by extraction, freed of boranes by treatment with hydrogen peroxide in methanol (23 °C, 2 h), and purified by sg chromatography to afford 85% yield of acetylenic lactones **11** (15-*S* and 15-*R* mixture). After THP cleavage the two acetylenic alcohols were separated chromatographically on sg and reduced (H_2, 1 atm, Lindlar catalyst) to **5** and the 15-*R* diastereomer, with the latter being recycled as described above.

The biological profiles of the C_{22}-PGs **7** and **8** are under active study. Preliminary results obtained in the laboratory of Prof. Peter W. Ramwell suggest that they are much less active on smooth muscle (guinea pig, rat) than $PGF_{2\alpha}$ and PGE_2. The methodology described herein allows the facile synthesis of PG_3s and should stimulate more detailed biological evaluation of this relatively neglected family of PGs. We have also utilized this approach for the synthesis of the C_{22}-PG_3s 19, 20-dihydro **7** and **8**.[13]

Supplementary Material Available: Spectroscopic data on compounds **1–9** and **11** (2 pages). Ordering information is given on any current masthead page.

(12) Zweifel, G.; Backlund, S. J.; Leung, T. *J. Am. Chem. Soc.* **1978**, *100*, 5561.

(13) This research was assisted financially by a grant from the National Science Foundation. The first preparation of **1** was performed in these laboratories by Dr. Haruhisa Shirahama (1970).

Stereoselective Generation of Acyclic Tetrasubstituted Enolates and Diastereoselective Aldol-Type Condensation

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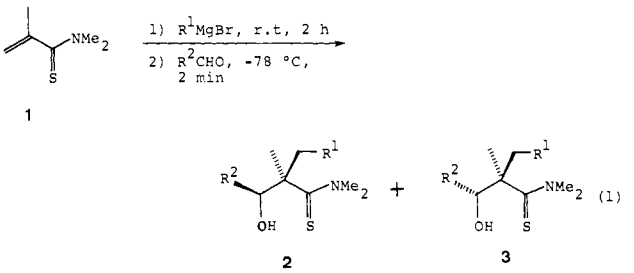
Received March 5, 1984

In recent years, the correlation between the structures of enolates and the stereochemical outcome in the aldol condensation has been well established.[1] Many elegant total syntheses of natural products owe their success to this methodology.[2] Interestingly, however, most of these are confined to reactions with the disubstituted (e.g., aldimine)[3] and trisubstituted (e.g., ester,[4] ketone,[5] etc.) enolates. As for the tetrasubstituted enolates, only a few examples have been reported with cyclic systems (α-substituted β-lactams,[6] γ-butylrolactones),[7] and only one example is known of an acyclic case (O-protected lactic acid ester).[8] The main reason for the scarcity of the tetrasubstituted enolate chemistry is due to the difficulty in preparing the stereochemically homogeneous enolates.

We wish to report the highly stereoselective aldol-type condensation with acyclic tetrasubstituted enolates, generated by the Michael addition of Grignard reagents to *N,N*-dimethyl-α-methacrylothioamide (**1**):[9] A THF solution of **1** (1 mmol in 10 mL of THF) was treated with 2 equiv of Grignard reagent at room temperature. After the solution was allowed to stir at this temperature for 2 h, the reaction mixture was cooled to −78 °C and an aldehyde (2 mmol) was added in one portion. After an appropriate time (see Table I), the reaction was quenched by the addition of 2 N HCl (eq 1). Results are summarized in Table I.



1 2 3

The yield and selectivity largely depend both on the kinds of Grignard reagents and aldehydes and may be classified into the following three groups. The first is the reaction of alkyl Grignards and alkyl aldehydes, which exclusively provides the erythro product **2** in good yield (entries 1–4). A thorough examination of the reaction mixture revealed that no detectable amount of threo isomer **3** was present (HPLC and ^1H and ^{13}C NMR). The threo isomer **3** (R^1 = Et, R^2 = *i*-Pr) was obtained in 10% yield, together with *N,N*-dimethyl-2-methylvalerothioamide (55%), at the complete expense of erythro **2** (R^1 = Et, R^2 = *i*-Pr), after allowing the reaction mixture of entry 2 to warm and stir at 0 °C for 3 h. The similar accumulation of **3** was also observed when similar conditions were used for R^1 = *i*-Pr, R^2 = Me (entry 3).[10] The second is the reaction of **1** with PhMgBr and alkyl or unsaturated aldehydes (entries 5–7). In these cases, the stereoselectivities are similarly high (>99%), but the yields are low. The residues of these reaction mixtures mainly consist of *N,N*-dimethyl-3-phenylisobutyrothioamide, and hence the low yields may be ascribed to diminished nucleophilicity of the enolate **7** (R^1 = Ph) toward the aldehyde carbonyl (cf. entry 11, eq 3).[11] The third is the reaction of the enolate **7** (irrespective of the kind of R^1) with benzaldehyde, which results in the nonstereoselective formation of **2** and **3** (entries 8, 10, and 11). The low selectivities in these runs may be due to a very facile retro-aldol, which seems to occur even at −78 °C, because the reaction of entry 10, when quenched at 2 s after addition of the aldehyde, showed a substantially increased erythro selectivity (**2**:**3** (R^1 = *i*-Pr, R^2 = Ph) = 50:50). The result in entry 9 (thermodynamic control) supports this explanation.

Although the experiments run under the conditions of thermodynamic control suggest that the product **3** is a sterically less hindered threo isomer, no conclusive evidences for the structure of **2** and **3** could be obtained from the attempted chemical

(1) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

(2) (a) Evans, D. A. *Ardrichimica Acta* **1982**, *15*, 23. (b) Masamune, S.; Choy, W. *Ibid.* **1982**, *15*, 47.

(3) Reetz, M. T.; Steinbach, R.; Kesseler, K. *Angew, Chem., Int. Ed. Engl.* **1982**, *21*, 864.

(4) (a) Meyers, A. I.; Reider, P. J. *J. Am. Chem. Soc.*, **1979**, *101*, 2051. (b) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975.

(5) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

(6) Hirai, K.; Iwano, Y.; Fujimoto, K. *Tetrahedron Lett.* **1982**, *23*, 4025.

(7) (a) Yamamoto, K.; Tomo, Y.; Suzuki, S. *Tetrahedron Lett.* **1980**, *21*, 2861. (b) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

(8) Heathcock, C. H.; Hagen, J. P.; Jarvi, E. T.; Pirrung, M. C.; Young, S. D. *J. Am. Chem. Soc.* **1981**, *103*, 4972.

(9) (a) Tamaru, Y.; Harada, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1978**, *100*, 5221; (b) *Ibid.* **1979**, *101*, 1316.

(10) HPLC (μ-Porasil, hexane–ethyl acetate 85:15 or 90:10) showed base-line separations for these **2** and **3**. The reaction with organolithium reagents showed somewhat diminished selectivity: the reaction of **1** with *n*-BuLi (−78 °C for 2 h then 0 °C for 2 h in THF) and acetaldehyde (−78 °C for 2 min) provided a mixture of **2** and **3** (R^1 = *n*-Bu, R^2 = Me) in a 90:10 ratio in 90% isolated yield, while the reaction of **1** with *n*-BuMgCl (room temperature for 1 day in THF) and acetaldehyde gave **2** (R^1 = *n*-Bu, R^2 = Me) exclusively in 91% isolated yield. All compounds reported showed satisfactory spectral and analytical data.

(11) The lower nucleophilicity of **7** (R^1 = Ph), compared with **7** (R^1 = alkyl), may be due to an intramolecular π-coordination of arenes to the counterion of enolate: Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.

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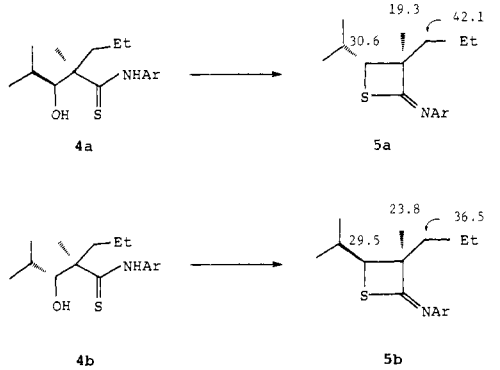
Table I. Tandem Michael Addition–Aldol Condensation of Thioamide **1**[a]

entry	Grignard, R^1MgBr	aldehyde, R^2CHO	conditions[b]	product distribution,[c] **2**:**3**	yield,[d] %
1	Et	Me	−78 °C, 2 min	>99:1	85
2	Et	*i*-Pr	−78 °C, 2 min	>99:1	86
3	*i*-Pr	Me	−78 °C, 2 min	>99:1	95
4	*i*-Pr	Et	−78 °C, 2 min	>99:1	86
5	Ph	Me	−78 °C, 2 min	>99:1	24
6	Ph	MeCH=CH	−78 °C, 2 min	>99:1	25
7	Ph	PhCH=CH	−78 °C, 2 min	>99:1	48
8	Et	Ph	−78 °C, 2 min	41:59	80
9	Et	Ph	−78 °C, 2 min; room temp, 18 h	8:92	80
10	*i*-Pr	Ph	−78 °C, 2 min	33:67	83
11	Ph	Ph	−78 °C, 2 min	17:83	81

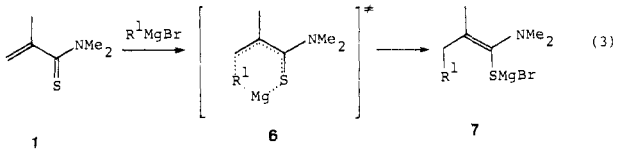
[a] For the structure of **2** and **3**, see eq 1. [b] Reaction conditions for the aldol condensation. [c] Distribution determined on the basis of HPLC, ^1H NMR, and/or ^{13}C NMR spectra. [d] Combined isolated yield of **2** and **3**.

transformations of **2** and/or **3** to the structurally defined authentic samples.[12] The structure of **2** and **3** was confirmed unequivocally by the procedure outlined in eq 2. *N*-(Trimethylsilyl)-*N*-(2,6-



dimethylphenyl)-α-methacrylothioamide (generated in situ by treatment of *N*-(2,6-dimethylphenyl)-α-methacrylothioamide with NaH/trimethylsilyl chloride in THF at 0 °C)[14] was subjected to a tandem Michael addition–aldol condensation[15] under conditions similar to those in Table I and gave a single aldol-type product of secondary thioamide (**4a**). The product **4a** was then subjected to the Mitsunobu reaction[16] and the β-thioiminolactone **5a** was obtained in quantitative yield. The trans structure of **5a** was determined on the basis of the observations of the higher field resonances of the α-methyl signal in the ^{13}C NMR spectra of **5a** compared with that of the cis isomer **5b**.[17,18] Selected data (figures given in ppm relative to Me_4Si) are shown in eq 2.

The high erythro selectivity might be attributed to the high *Z* stereochemical purity of the enolate **7**,[1] which may stem from the Michael addition of Grignard reagents to **1** through a coordination of magnesium(II) to the sulfur atom to form a 6π-electron cyclic transition state **6** (eq 3).[19] The usefulness of the present Michael



addition technique is furthermore augmented by the unsuccessful generation of tetrasubstituted enolate by treatment of *N*,*N*-dimethyl-2-methylvalerothioamide with bases (*i*-PrMgBr, *n*-BuLi, or LDA in THF either in the presence or absence of HMPA or TMEDA).[20]

(12) For example, **2** (R^1 = Ph, R^2 = Me) underwent a C_2–C_3 bond cleavage in the attempts to obtain the corresponding amine (MeI–$NaBH_4$ in *i*-PrOH: Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061). Similarly bond cleavage took place in the thiolactonization of **3** (R^1 = *i*-Pr, R^2 = Ph, excess formalin, 2 N HCl in THF reflux).[13] The attempted reduction of *N*,*N*-dimethyl-2-methyl-2-benzoylbutyrothioamide to **2** and/or **3** (R^1 = Ph, R^2 = Me) resulted in a C_2–C_3 bond cleavage, giving *N*,*N*-dimethyl-2-methylbutyrothioamide ($NaBH_4$ in *i*-PrOH or Na in EtOH at 0 °C).

(13) α-Monosubstituted β-hydroxy thioamides can easily be converted to 4-oxa-δ-thiovalerolactones. The details will be reported shortly.

(14) Tamaru, Y.; Amino, Y.; Furukawa, Y.; Kagotani, M.; Yoshida, Z. *J. Am. Chem. Soc.* **1982**, *104*, 4018.

(15) For the tandem conjugate addition–alkylation of unsaturated amides, see: (a) Baldwin, J. E.; Dupont, W. A. *Tetahedron Lett.* **1980**, *21*, 1881. (b) Mpango, G. B.; Mahalanabis, K. K.; Mahdavi-Damghani, Z.; Snieckus, V. *Ibid.* **1980**, *21*, 4823. For unsaturated ketones, see: (c) Heng, K. K.; Simpson, J.; Smith, R. A. J.; Robinson, W. T. *J. Org. Chem.* **1981**, *46*, 2932.

(16) Mitsunobu, O. *Synthesis* **1981**, 1.

(17) Levy, G. C.; Lichter, R. L.; Nelson, G. N. "Carbon-13 NMR Spectroscopy", 2nd ed.; Wiley: New York, 1980.

(18) A 1:1 mixture of **4a** and **4b** was obtained by the reaction of *N*-(2,6-dimethylphenyl)-α-methacrylothioamide with 3 equiv of ethyllithium (THF, −78 °C, 5 h) followed by treatment with 3 equiv of isobutylraldehyde (−78 °C, 2 min): Tamaru, Y.; Kagotani, M.; Yoshida, Z. *Tetrahedron Lett.* **1981**, *22*, 3409, 3413.

(19) (a) Tamaru, Y.; Harada, T.; Nishi, S.; Yoshida, Z. *Tetrahedron Lett.* **1982**, *23*, 2383. (b) Beak, P.; Hunter, J. E.; Jun, Y. M. *J. Am. Chem. Soc.* **1983**, *105*, 6350.

(20) We acknowledge partial support for this work provided by the Ministry of Education, the Japanese Government (Grant in Aid for Special Project Research 58110005 and Scientific Research B 58470066).

Oxidation of Hydroxide Ion by Immonium Oxide

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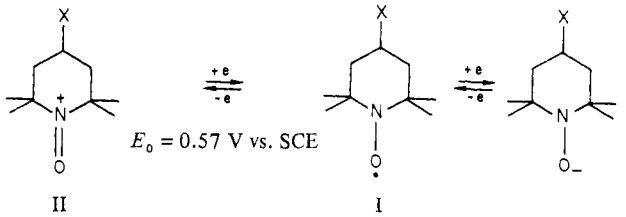
Received February 17, 1984

2,2,6,6-Tetramethylpiperidine-1-oxyl (I)[1] known as a stable radical has been widely used as a spin-labeling reagent in the field of biochemistry and applied as a spin trapping agent and antioxidant. A reversible redox system based on I is shown in eq 1.



1-Oxo-2,2,6,6-tetramethylpiperidinium salt (II)[1] used in this study is obtained by one-electron oxidation of I[2] with bromine.[3]

(1) Golubev, V. A.; Rozantsev, E. G.; Neiman, M. B. *Izv. Akad. Nauk SSSR* **1965**, 1927–1936.

0002-7863/84/1506-3877$01.50/0