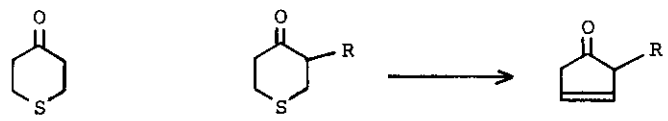
ENANTIOSELECTIVE SYNTHESIS OF 2,2-DISUBSTITUTED 3-CYCLOPENTENONE FROM 3-ALKYL-4-THIANONES

Haruo Matsuyama,* Yoshihiro Ebisawa, Michio Kobayashi,
and Nobumasa Kamigata
Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Setagaya-ku, Tokyo 158

Abstract——Enantioselective Synthesis of quaternary carbon centers through Michael-type alkylation of chiral imines of 3-methyl-4-thianone and successive regioselective synthesis of chiral 2,2-dialkyl-3-cyclopentenone via Ramberg-Bäcklund reactions are reported.

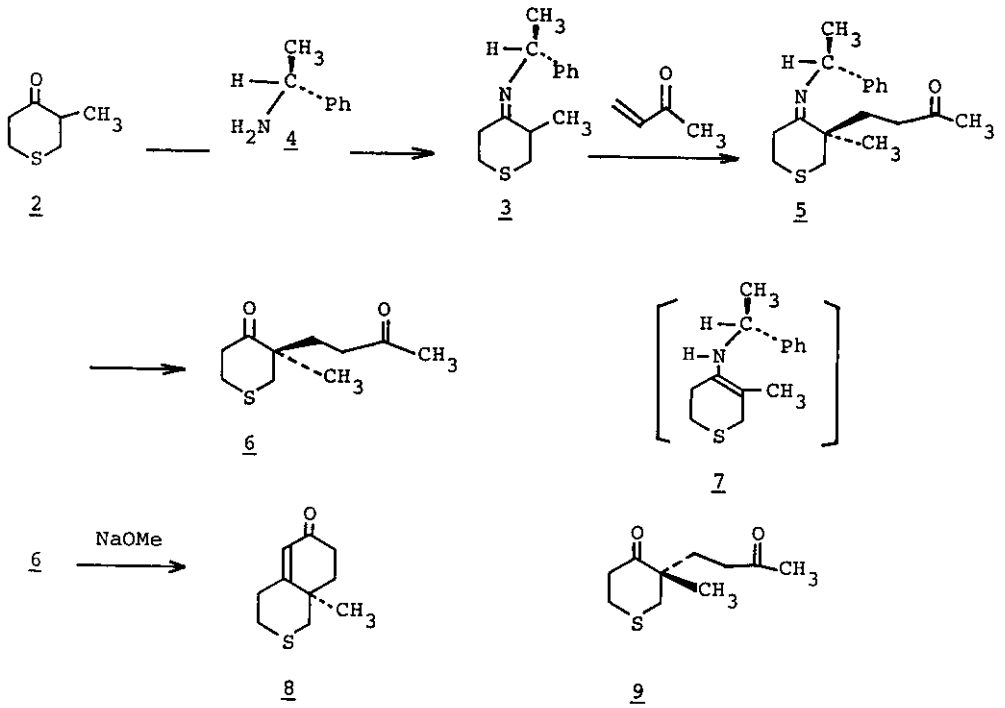
4-Thianone (1) is a heterocyclic compound consisted of five carbon units and a sulfur atom as an active functional group for a ring transformation. Recently we reported a regioselective synthesis of 2-alkyl-3-cyclopentenones starting from 4-thianone by the selective alkylation and Ramberg-Bäcklund type reactions.[1] We now describe studies on the use of these methods to the synthesis of an optically active 2-alkyl-3-cyclopentenone.



1 2

The reaction involves a new type of "deracemizing alkylation" [2] developed by Pfau et al. and we applied Pfau's procedure to imine derivatives of 3-alkyl-substituted 4-thianones (2) (Scheme 1). Thus reaction of imine 3, bp 139 °C (2 mmHg) [prepared in 63% yield from (±)-3-methyl-4-thianone (2) and (S)-(-)-1-phenylethylamine [3] 4 by azeotropic removal of water, toluene, p-toluenesulfonic acid (catalyst), 2 h] with 2 equiv. of methyl vinyl ketone (THF, 25 °C, 3 d) led to adduct 5. Hydrolysis (10% AcOH, 25 °C, 2 h) of crude compound 5 afforded (R)-(+)-diketone [4] 6, 61% yield, $[\alpha]_D^{20}$ +47.7° (c 0.98, EtOH), 65% ee, and the

starting amine 4. The enantiomeric excess of 6 was established by ^{1}H-nmr analysis in the presence of Eu(hfc)$_3$. The absolute configuration of 6 was determined in comparison with Pfau's report.[2] Clearly, the reactive nucleophilic spiecies in this reaction is the secondary enamine 7, in tautomeric equilibrium [5] with the imine 3, which reacts with methyl vinyl ketone regiospecifically [6] and stereoselectively. The stereoselectivity of this reaction can be explained by assuming a Diels-Alder like transition state (Figure 1).[7] Base-induced cyclization[8] of diketone 6 led to 8.[9] Similarly, (S)-(-)-diketone 9, 58% yield, $[\alpha]_D^{20}$ -47.2° (c 5.94, EtOH), 65% ee, was obtained starting from chiral imine 10, bp 150 °C (2 mmHg) [prepared in 76% yield from (±)-3-methyl-4-thianone and (R)-(+)-1-phenylethylamine [10] 11] with 1 equiv. of methyl vinyl ketone.



Scheme 1

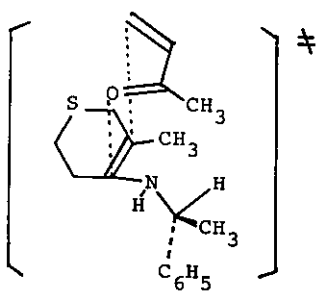
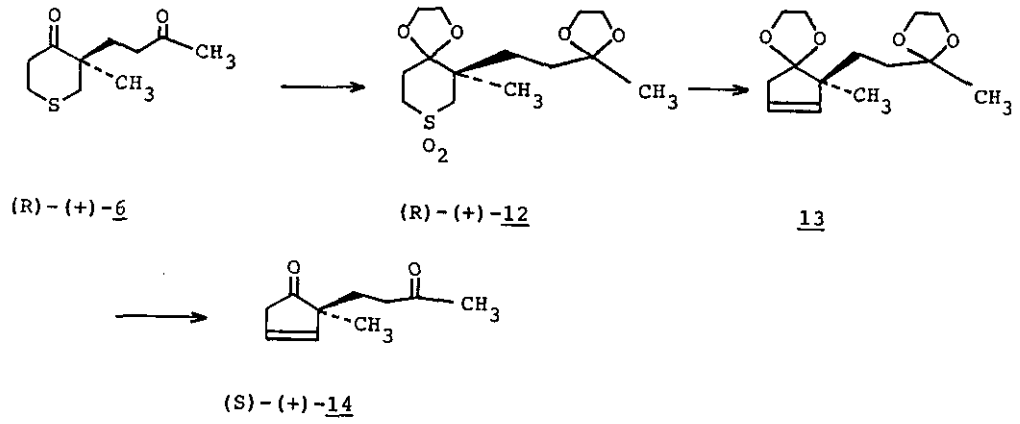


Figure 1.
Proposed transition state for the reaction of methyl vinyl ketone with chiral enamine (S)-7.

We attempted a synthesis of optically active 2,2-dialkyl-3-cyclopentenone from 6 as shown in Scheme 2. (R)-(+)-Diketone 6 was converted to 12 by protection of carbonyl group [ethylene glycol, p-toluenesulfonic acid (catalyst), benzene, reflux], followed by oxidation [m-chloroperbenzoic acid (3 equiv.)] in 79% yield.[11] Six-membered sulfone 12 was transformed into cyclopentene 13 by the one-pot Ramberg-Bäcklund reaction[1] (tert.-BuOK, CCl_4, tert.-BuOH, 50 °C) under nitrogen in 60% yield. After acid-catalyzed cleavage of the 1,3-dioxolane group in 13 [pyridinium p-toluenesulfonate (catalyst), aqueous acetone, reflux], optically active 3-cyclopentenone 14 [12] was obtained. Application of this procedure to natural compounds are in progress.



(R)-(+)-6 (R)-(+)-12 13

(S)-(+)-14

Scheme 2

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2. Asymmetric C-C bond forming reactions from tertiary carbon centers ("deracemizing alkylations"): U. H. Dolling, P. Davis, and E. J. J. Grabowski, J. Am. Chem. Soc., 1984, 106, 446. A. I. Meyers, M. Harre, and R. Garland, J. Am. Chem. Soc., 1984, 106, 1146. K. Tomioka, K. Ando, K. Takemasa, and K. Koga, J. Am. Chem. Soc., 1984, 106, 2718. M. Pfau, G. Revial, A. Guingant, and J. d'Angelo, J. Am. Chem. Soc., 1985, 107, 273.
3. Commercial amine 4, $[\alpha]_D^{20}$ -39.4° (neat), was used.
4. Purified by chromatography on silica gel, homogeneous by tlc and giving satisfactory ir and nmr spectra. 6: ^{1}H-Nmr ($CDCl_3$, 60 MHz) δ 1.15 (3 H, s),

2.10 (3 H, s), 2.35 (2 H, m), 2.50 - 3.00 (8 H, m containing s at 2.72); ir ($CDCl_3$) 1705 cm^{-1}; ms, m/z 200 (M^+); hrms, 200.0860 (Calcd for $C_{10}H_{16}O_2S$, 200.0871); cd $[\theta]_{299}$ +429 (EtOH). 3: $[\alpha]_D^{20}$ -38° (c 3.17, EtOH); ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.10 - 1.60 (6 H, m containing d at 1.30 (J= 6 Hz)), 2.20 - 3.00 (7 H, m), 4.63 (1 H, q, J= 6 Hz), 7.25 (5 H, s); ir 1650 cm^{-1}; ms, m/z 233 (M^+).

5. M. Pfau and C. Ribiere, J. Chem. Soc., Chem. Commun., 1970, 66. M. Pfau and C. Ribiere, Bull. Soc. Chim. Fr., 1971, 2584.
6. The alkylation takes place exclusively at the more substituted carbon atom; M. Pfau and J. U.-Monfrin, Tetrahedron, 1979, 35, 1899. P. W. Hickmott, Tetrahedron, 1982, 38, 3363.
7. R. Kober, K. Papadopoulos, W. Miltz, D. Enders, and W. Steglich, Tetrahedron, 1985, 41, 1693.
8. MeONa 5% in MeOH, 35 °C, 2 h, 53% yield.
9. 8: $[\alpha]_D^{20}$ -169° (c 0.64, EtOH); ir ($CDCl_3$) 1660 cm^{-1}; ms, m/z 182 (M^+); hrms, 182.0731 (Calcd for $C_{10}H_{14}OS$, 182.0765).
10. Commercial amine 11, $[\alpha]_D^{20}$ +38° (neat), was used.
11. 12: yield, 79%; $[\alpha]_D^{20}$ +1.54° (c 2.24, EtOH), $[\alpha]_{405}^{20}$ +2.3° (c 1.23, EtOH); ir ($CDCl_3$) 1320, 1300, 1290, 1130, 1110, 1090 cm^{-1}; ms, m/z 321 ($M^+ + 1$); hrms, 321.1463 (Calcd for $C_{14}H_{25}O_6S$, 321.1554).
12. 13: yield, 60%; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.05 (3 H, s), 1.30 (3 H, s), 1.60 (4 H, m), 2.50 (2 H, s), 3.90 (8 H, s), 5.65 (2 H, d, J= 3 Hz); ms, m/z 254 (M^+).

    14: yield, 85% from 13; $[\alpha]_D^{20}$+0.68° (c 0.59, EtOH); ir ($CDCl_3$) 1740, 1705 cm^{-1}; ms, m/z 166 (M^+); hrms, 166.0982 (Calcd for $C_{10}H_{14}O_2$, 166.0993).

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