HETEROCYCLES, Vol. 29, No. 3, 1989

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

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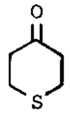
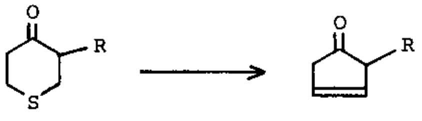
Abstract——Enantioselective Synthesis of quaternary carbon centers through Michael-type alkylation of chiral imines of 3-methyl-4-thianone and successive regioselective synthesis of chiral 2,2-dialkyl-3-cyclopentenone via Ramberg-Bäcklund reactions are reported.

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



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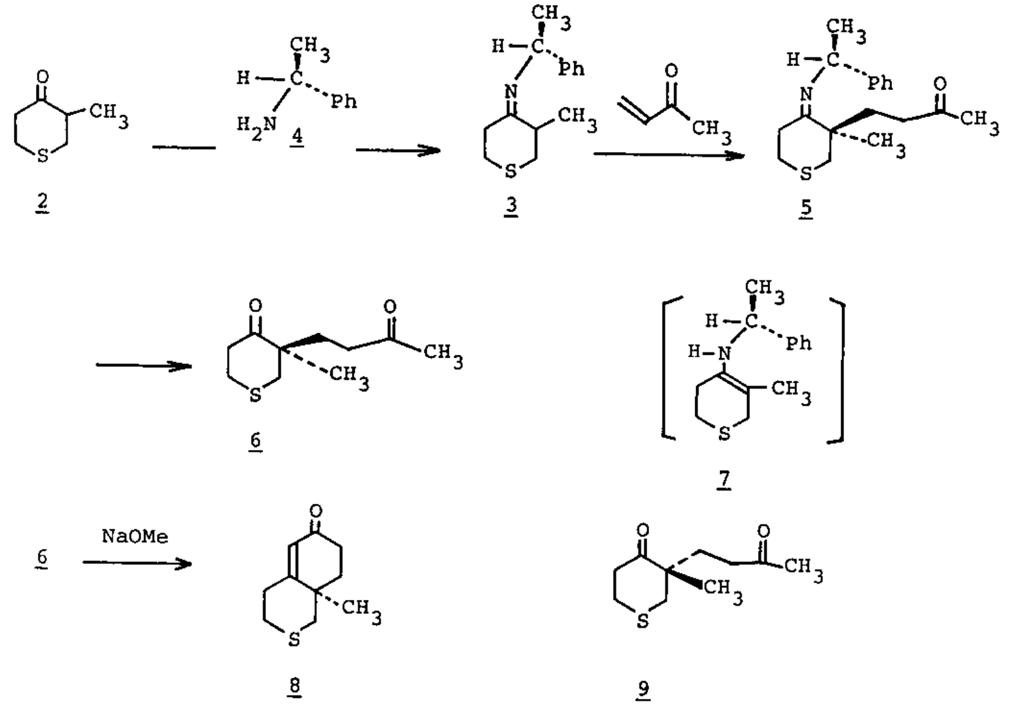
The reaction involves a new type of "deracemizing alkylation" [2] developed by Pfau et al. and we applied Pfau's procedure to imine derivatives of 3-alkyl-substituted 4-thianones (2) (Scheme 1). Thus reaction of imine 3, bp 139 °C (2 mmHg) [prepared in 63% yield from (±)-3-methyl-4-thianone (2) and (S)-(-)-1-phenylethylamine [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

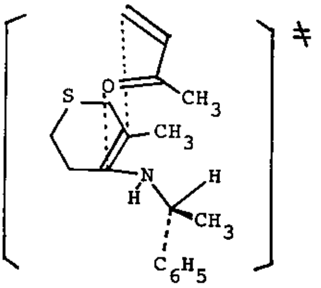
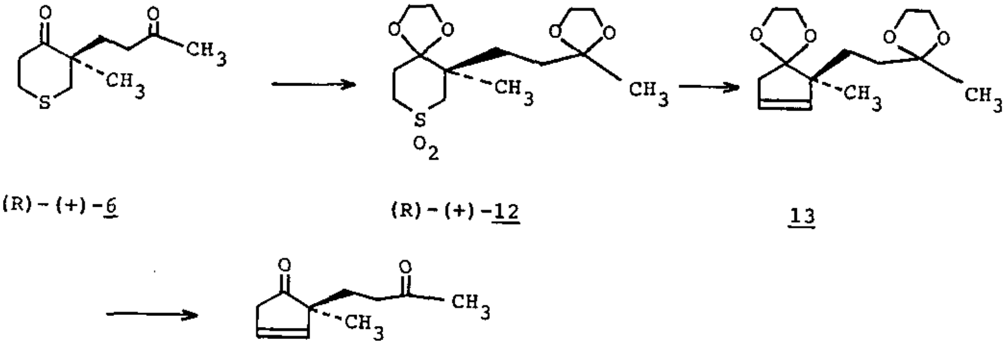


Figure 1.
Proposed transition state for the reaction of methyl vinyl ketone with chiral enamine (S)-7.

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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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); ^1H-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.
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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.
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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%; ^1H-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).

Received, 5th December, 1988