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NOVEL SYNTHESIS OF OPTICALLY ACTIVE LACTONES FROM 4-THIANONE

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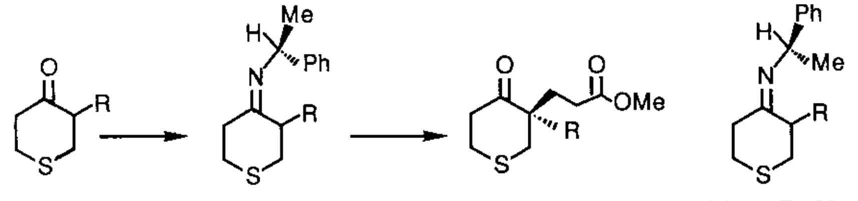
Abstract——Enantioselective synthesis (>92% e.e.) of quaternary carbon centers through Michael-type alkylation of chiral imines of 3-alkyl-4-thianones with methyl acrylate and successive diastereoselective synthesis of optically active lactones are described.

Considerable attention has been focused in recent years on cyclic sulfur compounds for the synthesis of interesting natural compounds[1] because sulfur-containing heterocycles are useful synthons in either ring expansion[2] or ring contraction[3] process. Recently we reported an enantioselective synthesis of 2,2-disubstituted 3-cyclopentenone from 3-alkyl-4-thianone via Ramberg-Bäcklund reactions.[4] We now describe studies on the synthesis of optically active lactones from 3-alkyl-4-thianones (1). The reaction involves a new type of "deracemizing alkylation" developed by Pfau et al.[5] and we applied their procedure to imine derivative of 3-alkyl-4-thianones. Thus reaction of chiral imine ((-)-3a (R= Me)) [prepared in 83% yield from (±)-3-methyl-4-thianone (1a) and (S)-(-)-1-phenylethylamine[6]] and 4 equiv. of methyl acrylate (DMF, 25 °C, 3 days then AcOH/10%-AcONa/ether= 1/5/6, 25 °C, 3 h) led to (R)-(+)-3-methyl-3-(2-methoxycarbonylethyl)-4-thianone (4a),[7] 61% yield, $[\alpha]_D^{25}$ +67.1° (c 1.11, EtOH), 92% ee,[8] and the starting amine (2). The absolute configuration of (+)-4a was tentatively assigned to be (R)-form in comparison with Pfau's report.[5] Similarly, keto ester ((S)-(-)-4a),[9] 14% yield, 92% ee, was obtained from chiral imine ((+)-3a) with methyl acrylate in THF. The chemical yields of quaternary carbon products increased to 60% when DMF was used as a solvent instead of THF. Stereoselective reduction of keto ester ((R)-(+)-4a) with 1 equiv. of sodium borohydride (-78 °C, ether/MeOH= 1/1, 15 min then 1% HCl, 30 min) afforded bicyclic lactones ((-)-5a, $[\alpha]_D^{25}$ -12.9° (c 0.99, EtOH), and (-)-6a, $[\alpha]_D^{25}$ -128° (c 0.87, EtOH)), as diastereomeric isomers (ratio, 5a/6a= 78/22) in 92% yield.[10] Performing the reduction with sodium borohydride in the presence of 1 equiv. of cerium trichloride[11] at -78 °C increased the amount of the stereoisomer (6a) (94% yield; ratio, 5a/6a= 61/39). Major stereoisomer (5a) was oxidized into the corresponding sulfone ((+)-7),[12] $[\alpha]_D^{25}$ +13.9° (c 0.81, CH_2Cl_2), with 3 equiv. of m-chloroperbenzoic acid in CH_2Cl_2, and the recrystallized compound ((+)-7) was then subjected to single-crystal X-ray structure analysis. The diffraction data were refined to an unweighted residual value of 0.040 for the structure (7) with the absolute configuration (C-3 and C-8 having the (R)-configuration).

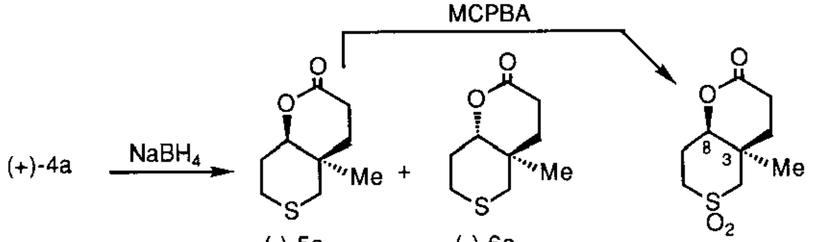


1a: R= Me
1b: R= $CH_2CH=CH_2$

(-)-3a: R= Me
(-)-3b: R= $CH_2CH=CH_2$

(+)-4a: R= Me
(+)-4b: R= $CH_2CH=CH_2$

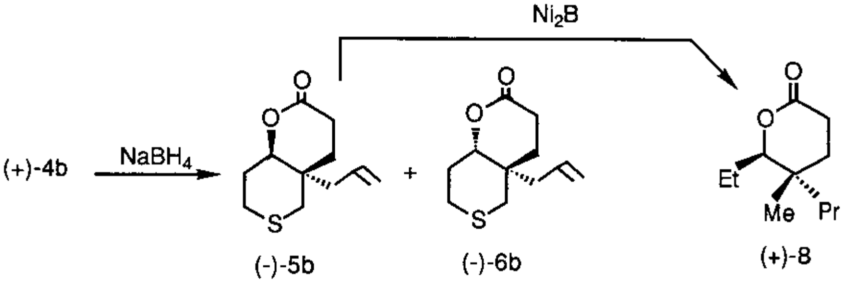
(+)-3a: R= Me
(+)-3b: R= $CH_2CH=CH_2$



(-)-5a (-)-6a (3R,8R)-(+)-7

5a/6a= 78/22

Next, chiral imine ((-)-3b (R= allyl)) was reacted with 5 equiv. of methyl acrylate in DMF at 25 °C for 5 days to give (S)-(+)-3-allyl-3-(2-methoxycarbonylethyl)-4-thianone ((4b) (R= allyl))[13] [23% yield, $[\alpha]_D^{25}$ +17.0° (c 1.83, EtOH), 95% ee]. Similarly, keto ester ((R)-(-)-4b (R= allyl)), 8% yield, 95% ee, was obtained from the reaction of the imine ((+)-3b (R= allyl)) and methyl acrylate in THF. When keto ester ((S)-(+)-4b) was reduced with 1 equiv. of sodium borohydride (25 °C, MeOH, 2.5 h then 1% HCl, 0.5 h), the corresponding lactones (5b, $[\alpha]_D^{25}$ -19.4° (c 1.34, CH_2Cl_2), and 6b, $[\alpha]_D^{25}$ -59.2° (c 0.32, CH_2Cl_2)), were obtained in 42% yield (ratio, 5b/6b= 80/20).[14] We then attempted to convert the C-S bonds of bicyclic lactone ((-)-5b) into C-H bonds with a variety of nickel reagents (e.g. Raney Ni, nickel boride). Nickel boride,[15] conveniently generated in situ from nickel chloride hexahydrate and sodium borohydride in MeOH-THF at 0 °C, has been used to desulfurize major stereoisomer ((-)-5b) to the corresponding lactone ((+)-8)[16] [43% yield, $[\alpha]_D^{25}$ +85.3° (c 0.27, EtOH)]. The compounds reported herein will be useful as optically active synthons for the synthesis of interesting natural compounds, and the further studies along this line are in progress.



5b/6b= 80/20

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4. H. Matsuyama, Y. Ebisawa, M. Kobayashi, and N. Kamigata, Heterocycles, 1989, 29, 449.
5. M. Pfau, G. Revial, A. Guingant, and J. d'Angelo, J. Am. Chem. Soc., 1985, 107, 273 and references cited therein.
6. Commercial amine (S)-(-)-2, $[\alpha]_D^{20}$ -39.4° (neat), was used.
7. Purified by gel-permeation chromatography using a JAI LC-08 liquid chromatograph with two JAIGEL-1H columns (20mm x 600mm) with chloroform as eluent. (R)-(+)-4a: oil; hrms, 216.0866 (Calcd for $C_{10}H_{16}O_3S$, 216.0820); cd $[\theta]_{299}$ +1130 (c 0.052, EtOH). (-)-3a: bp 141-145 °C (3 mmHg); $[\alpha]_D^{25}$ -35.3° (c 1.05, EtOH); ir (neat) 1655 cm^{-1} (C=N); ms, m/z 233 (M^+), 218, 200, 191.

8. The enantiomeric excess of (+)-4a was determined by HPLC measurement using optically active column (DAICEL CHIRALPAK AD; hexane/EtOH= 9/1).

9. (S)-(−)-4a: oil; hrms, 216.0813 (Calcd for $C_{10}H_{16}O_3S$, 216.0820); cd $[\theta]_{299}$ −908 (c 0.045, EtOH).

10. Lactone (3R,8R)-(−)-5a: oil; ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.27 (3H, s), 1.67-3.17 (10H, m), 4.13 (1H, t, J= 4.0 Hz); ^{13}C-nmr ($CDCl_3$) δ 23.09, 23.93, 26.73, 29.07, 31.48 (s), 31.87, 34.34, 81.81, 171.03; ir (neat) 1725 cm^{-1}; hrms, 186.0680 (Calcd for $C_9H_{14}O_2S$, 186.0714); cd $[\theta]_{235}$ −498 (c 0.053, EtOH); tlc (silica gel) R_f= 0.30 (hexane: ether= 1:1). (3R,8S)-(−)-6a: oil; ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.23 (3H, s), 1.50-2.90 (10H, m), 3.80-4.07 (1H, m); ^{13}C-nmr ($CDCl_3$) δ 15.15, 27.51, 28.03, 28.81, 33.95 (s), 34.79, 40.58, 83.69, 170.25; ir (neat) 1730 cm^{-1}; hrms, 186.0698 (Calcd for $C_9H_{14}O_2S$, 186.0714); cd $[\theta]_{251}$ +53, $[\theta]_{245}$ 0, $[\theta]_{228}$ −607 (c 0.047, EtOH); tlc (silica gel) R_f= 0.26 (hexane: ether= 1:1).

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12. (3R,8R)-(+)-7: colorless needles; mp 192-194 °C (from EtOH); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.40 (3H, s), 1.50-3.67 (10H, m), 4.23 (1H, t, J= 3.0 Hz); ir(KBr) 1720, 1320, 1120 cm^{-1}; hrms, 218.0582 (Calcd for $C_9H_{14}O_4S$, 218.0613).

13. (S)-(+)-4b: oil; hrms, 242.0989 (Calcd for $C_{12}H_{18}O_3S$, 242.0976); cd $[\theta]_{296}$ −330 (c 0.038, EtOH); $[\alpha]_{435}$ +48.9° and $[\alpha]_{546}$ +20.8° (c 1.03, EtOH).

14. (3S,8R)-(−)-5b: oil; ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.20-3.20 (12H, m), 4.17 (1H, t, J= 4.0 Hz), 4.93-6.13 (3H, m); ^{13}C-nmr ($CDCl_3$) δ 22.89, 26.73, 28.61 (2 x C), 32.65, 34.34 (s), 39.47, 80.18, 119.85, 131.69, 171.16; ir (neat) 1740, 1640 cm^{-1}; ms, m/z 212 (M^+), 197, 184, 170, 156; hrms, 212.0838 (Calcd for $C_{11}H_{16}O_2S$, 212.0871); cd $[\theta]_{237}$ −738 (c 0.063, CH_2Cl_2); tlc (silica gel) R_f= 0.26 (hexane: ether= 1:1). (3S,8S)-(−)-6b: oil; hrms, 212.0842 (Calcd for $C_{11}H_{16}O_2S$, 212.0871); cd $[\theta]_{232}$ −591 (c 0.015, CH_2Cl_2); tlc (silica gel) R_f= 0.19 (hexane: ether= 1:1).

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16. Lactone (+)-8: oil; ^{1}H-nmr (90 MHz, $CDCl_3$) δ 0.91-0.93 (6H, m containing s at 0.91), 1.07 (3H, t, J= 6.6 Hz), 1.27-1.79 (8H, m), 2.53 (2H, t, J= 7.4 Hz), 3.91 (1H, dd, J= 8.8 and 2.9 Hz); ir (neat) 1730 cm^{-1}; ms, m/z 184 (M^+), 155, 149, 141, 126, 108; hrms, 184.1460 (Calcd for $C_{11}H_{20}O_2$, 184.1464).

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