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ENANTIOCONTROLLED SYNTHESIS OF (S)-3-SUBSTITUTED CYCLOALKANONES FROM (S)-2-(p-TOLYLSULFINYL)-2-CYCLOALKENONES AND DIORGANOMAGNESIUM REAGENTS.

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Summary: By appropriate choice of reaction conditions, the same enantiomerically pure (S)-(+)-2-(p-tolylsulfinyl)cycloalkenone can be converted into either an (R)- or an (S)-3-substituted cycloalkanone in good to excellent enantiomeric purity.

Many enantiomerically pure cycloalkanones substituted at the 3-position with hydrocarbon groups are not only important synthetic intermediates but are also physiologically active natural products. For example, fragrant methyl jasmonate,[1] antibiotic sarkomycin,[2] and the E-series of prostaglandins[3] are all (R)-3-substituted cyclopentanones, and the plant stress metabolite solavetivone[4] is an (R)-3-methylcyclohexanone. Similarly, anti-tumor pseudoguaianolide damsin,[5] antibiotic methylenomycin,[6] and 17-oxo-steroidal estrogens[7] are (S)-3-substituted cyclopentanones, and anti-tumor eudesmanolide pinnatifidin[8] is an (S)-3-methylcyclohexanone. We recently have introduced enantiomerically pure (S)-(+)-2-(p-tolylsulfinyl)-2-cyclopentenone and -cyclohexenone[9] for use in effective synthesis of various (R)-3-substituted cycloalkenones of very high enantiomeric purity. The absolute stereochemistry of this 1,3-sulfur → carbon asymmetric induction was rationalized using a chelate model.[9] We now have discovered that, under different reaction conditions, the same cycloalkenone sulfoxides can be used also to generate the antipodal (S)-3-substituted cycloalkanones and that this is a reliable and general procedure allowing enantiocontrolled attachment not only of methyl,[9b] but also of n-alkyl, sec-alkyl, vinyl, and aryl groups at the 3-position of 5- and 6-membered cycloalkanones. We rationalize the results shown in Table I in terms of a non-chelate model in which the individual bond dipoles of the sulfinyl and the carbonyl groups of these β-ketosulfoxides are oriented in opposite directions,[10] thus allowing the tolyl group to shield the re-diastereotopic face of C-3 and to direct approach of the nucleophilic diorganomagnesium reagents preferentially or exclusively from the si-face. The apparently weak

Lewis-acidity of diorganomagnesium species (and thus their apparently weak or non-existent complexation with our β-ketosulfoxides) has been invoked before to explain the configurational stabilities of organomagnesium reagents[11] as well as to rationalize product distributions from reactions of organomagnesium reagents with ketones[12] and epoxides.[13]

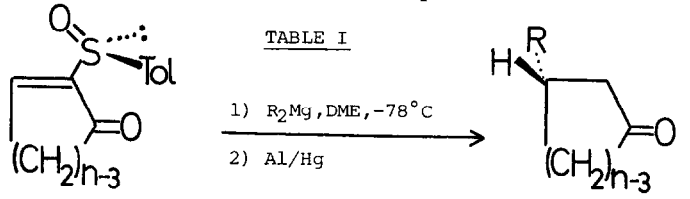

TABLE I

Entry	n	R	% Yield	% e.e.
1	5	Methyl	69[a,b,c]	97[d]
2	5	Ethyl	88	81[e]
3	5	Neopentyl	77[b]	91[e]
4	5	Vinyl	74[b]	57[e]
5	5	Phenyl	72[c]	>98[e]
6	6	Methyl	67[b]	79[d]
7	6	i-Propyl	53[b]	50[e]
8	6	sec-Butyl[c]	67[b]	62[e,f]

a. Isolated as the 2,4-dinitrophenylhydrazone; b. One equivalent of 18-crown-6 was used also; c. THF was used as a solvent; d. Determined by polarimetry; e. Determined by ^{13}C NMR spectroscopy of the corresponding (R,R)-(−)-2,3-butanediol ketals:(see ref. 21); f. At C-3 of the cyclohexanone only.

Several features of the results shown in Table I are noteworthy: (1) First, conjugate addition of a phenyl group (entry 5) has occurred reproducibly with extremely high asymmetric induction (> 99:1 ratio of S:R enantiomers); (2) this degree of absolute stereocontrol is substantially better than that observed using zinc dibromide and phenylmagnesium chloride which leads to the antipode, (R)-3-phenylcyclopentanone, in 92% e.e.[14]; (3) in several cases, a highly complexing additive such as 18-crown-6 served to raise the amount of asymmetric induction by about 20%; and (4) the degree of stereocontrol in the cyclopentenone series is somewhat better than in the cyclohexenone series possibly due to the less rigid nature of the latter.

Taken together with our previous findings,[9,14] these results clearly indicate that either enantiomer of many different 3-substituted cyclopentanones and cyclohexanones can be prepared

effectively in good to excellent enantiomeric purity from the same enantiomerically pure 2-(p-tolylsulfinyl)-2-cycloalkenone.[14-17] Once absolute stereochemistry is established at the 3-position, subsequent chemical transformations can proceed with high or even complete induction of asymmetry to other positions of the ring system.[9]

Such flexibility and efficient use of these enantiomerically pure 2-sulfinylcycloalkenones make them highly significant, attractive, and promising intermediates in asymmetric synthesis of complex organic compounds. We are actively pursuing various applications of this new methodology.

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18. A representative procedure follows: a dry 25 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber serum stopper was flushed with nitrogen and charged with 106.8 mg (0.48 mmol) of (S)-(+)-2-(p-tolylsulfinyl)-2-cyclopentenone and 3.0 mL of 1,2-dimethoxyethane. After the stirred solution had been cooled to -64°C, 300 μL (0.60 mmol) of 2.0 M diethylmagnesium[19] was added dropwise via syringe. The reaction was stirred at -64°C for 1.5h, then was warmed to 0°C and the solvents removed in vacuo at 0°C. About 10 mL of a 0°C 9:1 THF:H_2O solution was added and the resultant solution cooled to -15°C. Aluminum amalgam[20] made from 120 mg (4.4 mmol) of aluminum foil was added and the reaction was stirred overnight under nitrogen while the cooling bath was allowed to slowly warm to room temperature. Normal work-up and preparative tlc gave 48.0 mg (88%) of (S)-(−)-3-ethylcyclopentanone, $[\alpha]_D^{25} = -90.5°$ (c 0.19, $CHCl_3$). 46.0 mg (0.41 mmol) of the ketone was ketalized using 75 μL (0.82 mmol) of (R,R)-(−)-2,3-butanediol and 1 mg of p-toluenesulfonic acid in a total volume of ca. 12 mL of benzene; after refluxing overnight with azeotropic removal of water, the reaction was cooled to room temperature and the benzene was removed by rotary evaporation. Normal work-up gave 43.7 mg (59%) of the corresponding ketal: Anal. Calcd. for $C_{11}H_{20}O_2$: C,71.70; H,10.94%. Found: C,71.91; H,10.65%. Relative integrations of the diastereotopic carbon resonances at 39.64 and 39.12 ppm in the ^{13}C NMR spectrum of this ketal indicated 81% diastereomeric excess. According to the literature[21] and our own experience, preparative tlc is incapable of separating the diastereomers formed from racemic 3-alkylcycloalkanones and (R,R)-(−)-2,3-butanediol.

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