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ENANTIOSELECTIVE MICHAEL REACTIONS.
STEREOSELECTIVE ADDITION OF ENOLATES OF PHENMENTHOL ESTERS TO CROTONATES

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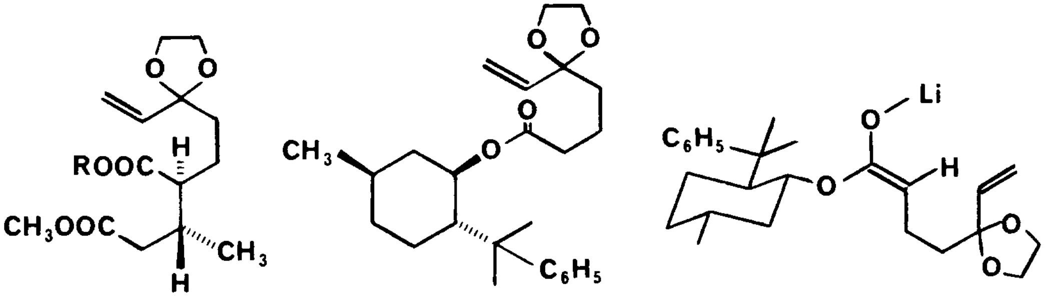
Summary: A method is described for enantioselective synthesis which is based on the stereoselective Michael addition of phenmenthol enolates such as 5 to E-crotonate esters. A stereomechanistic rationale is presented.

In connection with a projected synthesis of a natural product of marine origin it was required to produce as a key intermediate the ketal 1 with assured absolute configuration. An attractive possibility for



1 2 3

the synthesis of 1 appeared to be the Michael reaction of the Z-enolate 3 derived from phenmenthol[1] ester 2 with either E- or Z-methyl crotonate. Impressive diastereoselectivity has been demonstrated previously by J. Mulzer and co-workers[2] for the reaction of β-lactone enolates with dimethyl maleate and by M. Yamaguchi and co-workers for the reaction of t-butyl esters with E-crotonates.[3,4] On the basis of these studies[2,3] it was surmised that the Z-enolate 3 (derivable from 2 by the action of lithium diisopropylamide in tetrahydrofuran at -78°[5]) would react with E-methyl crotonate by predominant si/si-face coupling to form 1, R = phenmenthyl, as major product. The course of the reaction of 3 with Z-methyl crotonate, which seemed less clear, was of equal interest because of its bearing on the stereomechanistic possibilities for these Michael reactions. This note reports the outcome of initial investigations in this area which were carried out with the propionate esters of (-)-menthol and (-)-phenmenthol and the E- and Z-methyl crotonates. The use of propionate esters facilitated the determination of absolute configuration by allowing correlation with known substances.

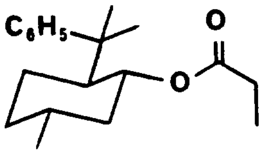
(-)-Phenmenthol was prepared from commercial (+)-pulegone as described previously[1] and converted to the propionate ester 4 by reaction with propionyl chloride and pyridine (1.5 equiv of each in benzene at 24° for 2 hr).[6] Conversion of 4 to the lithium enolate 5 was effected by treatment with 1.1 equiv of lithium diisopropylamide in tetrahydrofuran (THF) at -78° for 30 min and the resulting solution was cooled to -100° (ether-liquid nitrogen bath) and treated with E-methyl crotonate. After 3 hr at -100° the reaction mixture was quenched (HOAc in THF) and the product was isolated by extraction and flash chromatography on silica gel using 9 : 1 hexane-ethyl acetate. Analysis of the product (75-79% total yield) by capillary gas chromatography (cgc) using a 30-m DB-1 column (J and W Scientific Co.) (200°, 19 psi carrier pressure) revealed 4 well-resolved components with retention times 5.26, 5.73, 6.69 and 7.43 min. The first two peaks were diastereomeric esters of erythro 2, 3-dimethylglutaric acid and the last two were diastereomeric esters of the desired threo 2, 3-dimethylglutaric acid.[7] The ratio of threo to erythro adducts was 90 : 10 and within the threo pair the ratio of diastereomers was 95 : 5. That the major diastereomer (7.43 peak) was the expected threo ester 6 was shown in the following way.

The mixture of Michael adducts from 5 and E-methyl crotonate was subjected to the transformations summarized for the principal component 6 in Scheme A. For 6 the sequence was: (1) enolate formation (1.1 equiv of lithium diisopropylamide in THF at -78°)followed by quenching with 5 equiv of chlorotrimethylsilane to give the silyl ketene acetal 7; (2) ozonolysis in methylene chloride at -78° for 10 min, oxidative workup with excess peracetic acid in ethyl acetate at -78° to 24° for 1 hr and at 24° for 12 hr, and esterification with diazomethane to form diester 8; (3) transesterification to dimethyl dimethylsuccinate 9 by heating at reflux for 115 hr with 20% methanesulfonic acid in methanol; and (4) saponification (1 N lithium hydroxide-THF-H_2O-CH_3OH at 24° for 1 hr), isolation of the diacid, and cyclization to 2, 3-dimethylsuccinic anhydride by reaction with trifluoroacetic anhydride at 0° for 1 hr. The 2, 3-dimethylsuccinic anhydride isolated had $[\alpha]_D^{24}$ + 90.7° (c = 4.5, C_6H_6) indicative of the 2R, 3R configuration as in 10. The stereochemistry and absolute configuration of the major Michael adduct 6 is therefore established.[8]

The reaction of the lithium enolate 5 in THF at -100° with Z-methyl crotonate was slower than the corresponding process with E-methyl crotonate and after 3 hr only 54% of Michael addition had occurred. The isomeric products (4 total) from 5 and Z-methyl crotonate were mainly erythro, the overall erythro-threo ratio being 75 : 25. The ratios of diastereomers was 87 : 13 for the erythro pair and 52 : 48 for the threo pair. Thus the major Michael pathway with enolate 5 depends crucially on the E or Z geometry of the crotonate acceptor, with E-crotonate favoring threo by 90 : 10 and Z-crotonate favoring erythro, but only by 75 : 25.

The Michael reaction of the lithio enolate analogous to 5 but derived from (-)-menthol was also examined using E-methyl crotonate as substrate. At -100° in THF (total yield 80%) the threo : erythro product ratio was 88 : 12 and the selectivity between the two diastereomeric threo esters was 78 : 22. It is clear from this result that the phenmenthol controller group is definitely more effective than menthol, in accord with previous experience.[1] Neomenthol (the axial OH epimer of menthol) was less effective than menthol (threo : erythro ratio 80 : 20; diastereoselectivity 67 : 33 for threo and 1 : 1 for erythro products).

A clear stereo-mechanistic picture emerges from the knowledge of reaction products obtained from phenmenthol lithium enolate 5 and E- and Z-methyl crotonates. As expected from the strong steric screening due to the 2-phenyl-2-propyl substituent,attack by crotonate occurs at the si face of 5. More interesting is the finding that the si face of 5 selects for attack the si face of E-methyl crotonate but the re face of



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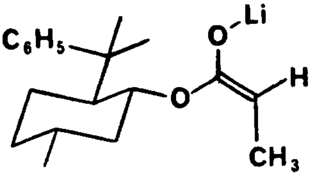

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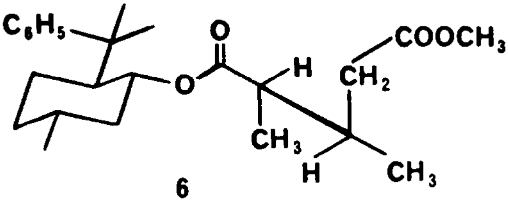

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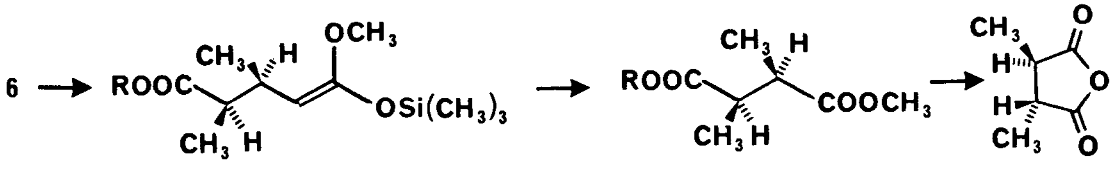
Scheme A:



7, R = PhM

8, R = PhM

9, R = CH_3

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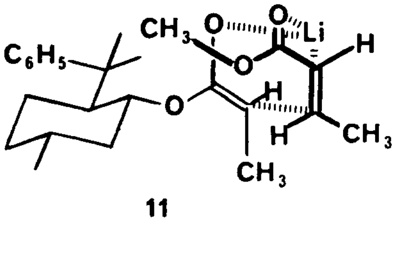
PhM = Phenmenthol

Z-methyl crotonate. This reversal strongly suggests a crucial role for the carbomethoxy group of crotonate and therefore implicates it as a lithium-ion coordinating group. In consequence it seems reasonable that the major pathway for the E-crotonate reaction involves complex 11 and the major pathway for the Z-crotonate reaction involves complex 12.



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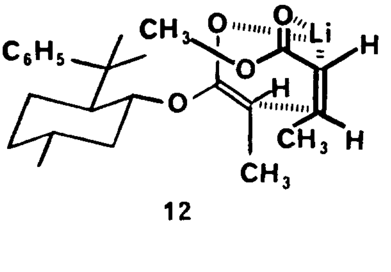

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The enantioselective Michael addition methodology described herein can in all probability be improved further by the use of other controller groups and work is continuing along these lines. It is clear from the present results that the enantioselective synthesis of 5-oxo esters by this methodology promises to be both practical and of broad scope.[9,10]

References and Notes

1. E. J. Corey and H. E. Ensley, J. Am. Chem. Soc., 97, 6908 (1975); H. E. Ensley, Ph.D. dissertation, Harvard University, 1976. 8-Phenylmenthol is referred to herein as phenmenthol.
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3. M. Yamaguchi, M. Tsukamoto, S. Tanaka, and I. Hirao, Tetrahedron Letters, 25, 5661 (1984).
4. M. Yamaguchi, M. Tsukamoto, and I. Hirao, ibid., 26, 1723 (1985).
5. R. E. Ireland, R. M. Mueller, and A. K. Willard, J. Am. Chem. Soc., 98, 2868 (1976).
6. New compounds were characterized by 270 MHz pmr, infrared and mass spectroscopy. All reactions involving air-sensitive compounds or intermediates were conducted under nitrogen.
7. For identification we used transesterification with methanolic methanesulfonic acid at reflux and comparison by cgc with authentic samples of threo and erythro 2,3-dimethylglutaric acid dimethyl esters.
8. (a) E. Berner and R. Leonardson, Ann. Chem., 538, 1 (1939); (b) B. Carnmalm, Chem. and Ind. (London), 1093 (1956).
9. We thank Drs. Plato Magriotis and David Evans for helpful discussions. Dr. Magriotis has demonstrated the stereoselective synthesis of **1** by the methodology described herein (to be published as part of a total synthesis of diisocyanoadocianes).

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