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A HIGHLY STEREOSELECTIVE SYNTHESIS OF CARBOCYCLIC COMPOUNDS BY THE MICHAEL INDUCED INTRAMOLECULAR ALKYLATION A STEREOCONTROL OF EXTRACYCLIC CHIRAL CENTERS

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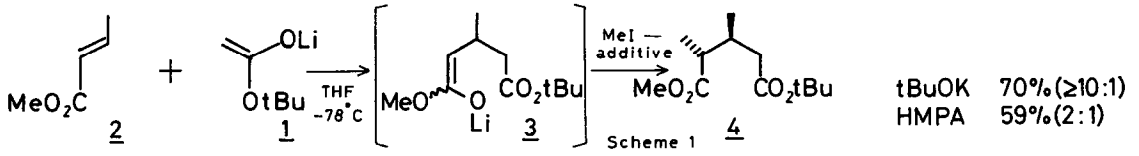
Abstract: Three, five, six, and seven-membered carbocyclic compounds, some of which contain an extracyclic chiral center, were synthesized highly stereoselectively by the Michael induced intramolecular alkylation.

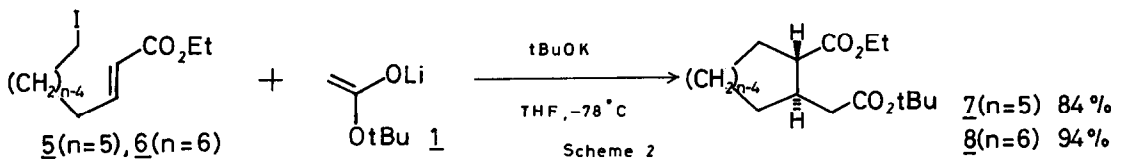
Previously, we have reported that the Michael addition of simple ester enolates to α,β-unsaturated esters proceeds smoothly to give glutarates in high yields.[1] As this Michael reaction initially affords lithium enolates of glutarates, we planned to utilize this anionic intermediate. At first, lithiated t-butyl acetate (1) was reacted with 1.0 equivalent of methyl crotonate (2) in THF at -78 °C, and the resulted lithium enolate of 3-methylglutarate 3 was treated with excess methyl iodide at -78 °C. Unexpectedly, the methylation did not occur at all, and only t-butyl methyl 3-methylglutarate was isolated. This suggests that lithiated glutarate 3 exists in an unreactive state. In order to activate 3, additives were introduced prior to methyl iodide. Potassium t-butoxide and HMPA were found to be effective. Especially, the former gave 3,4-dimethylglutarate 4 with threo-configuration in ≥10:1 selectivity[2] (Scheme 1).



Scheme 1

Based on these observations, the Michael induced intramolecular alkylation was examined. Thus, ethyl 6-iodo-2-hexenoate (5) and ethyl 7-iodo-2-heptenoate (6) were treated with 1 in the presence of potassium t-butoxide in THF at -78 °C, and the corresponding five and six-membered cyclic compounds 7 and 8 were obtained in high yields (Scheme 2). The ^{13}C-NMR spectra of 7 and 8 show that the products consist of a single isomer. The configuration of the two side chains was determined to be trans by converting to the known compounds.[3]

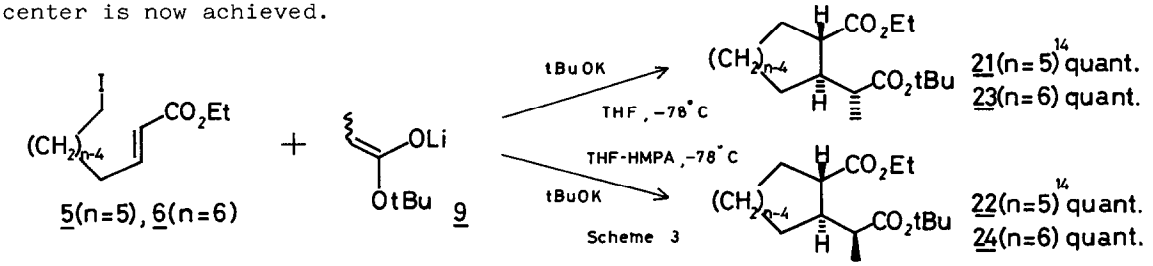
A typical procedure is described for the synthesis of t-butyl trans-2-ethoxycarbonyl-1-cyclopentanepropionate (7): Under a nitrogen atmosphere, to



Scheme 2

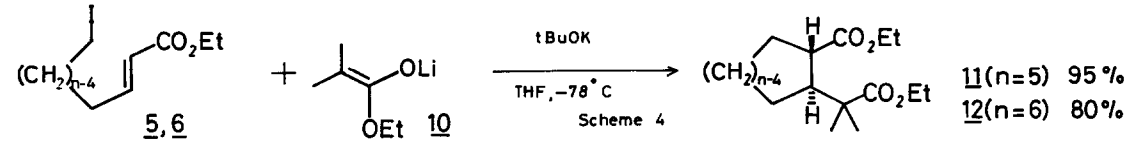
a THF-hexane (1.5+1 mL) solution of LDA (1.5 mmol) was added a THF (1.5 mL) solution of t-butyl acetate (175 mg, 1.5 mmol) at -78 °C. After 30 min, potassium t-butoxide (169 mg, 1.5 mmol) in THF (2.5 mL) was added and the mixture was stirred for 10 min. Then, 5 (133 mg, 0.5 mmol) in THF (1.5 mL) was added and the reaction was continued for 30 min at -78 °C. Saturated aqueous ammonium chloride was added, and organic materials were extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. A short-path distillation at 105 °C/0.5 mm gave 7 (107 mg, 84%). ^{1}H-NMR ($CDCl_3$-CCl_4) δ 1.25 (3H,t,J=7Hz), 1.43 (9H,s), 1.6-2.0 (6H,m), 2.0-2.6 (4H,m), 4.11 (2H,q,J=7Hz). ^{13}C-NMR ($CDCl_3$-CCl_4) δ 14.2, 24.5, 28.0, 29.9, 32.3, 40.4, 40.5, 49.5, 59.9, 79.7, 171.1, 175.1. IR (neat) 1720 cm^{-1}.

Recently, it was found that using THF or THF-HMPA (4:1) as the solvent lithium enolate of t-butyl propionate (9) adds to β-monosubstituted α,β-unsaturated esters to give threo- and erythro-disubstituted glutarates, respectively.[4] Thus, 5 and 6 are reacted with 9 in THF or THF-HMPA, and each stereoisomer is obtained in ≥15:1 selectivity in quantitative yields. The stereochemistry of the isomers is determined as shown below based on the previous study[4] and the trans-relation of the side chains in 7 and 8 (Scheme 3). Stereochemical controll of three asymmetric centers including an extracyclic chiral center is now achieved.



Scheme 3

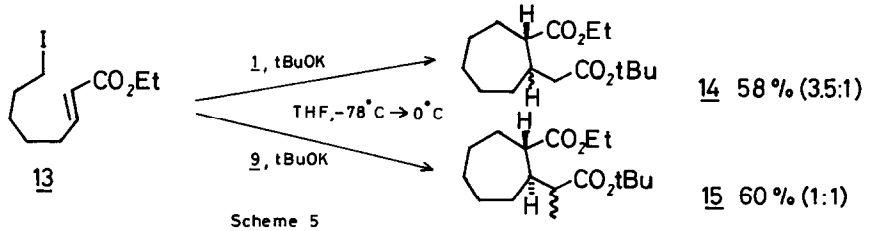
Lithiated ethyl isobutyrate (10) was also subjected to the cyclization, and α,α-dimethylcycloalkanepropionate 11 and 12 were obtained in high yields (Scheme 4).



Scheme 4

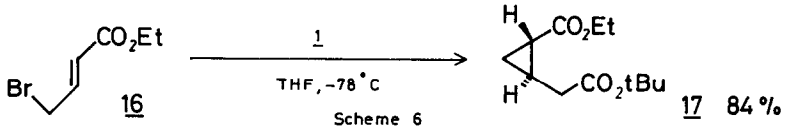
The seven-membered ring formation met with some difficulties because of the sluggishness. The major problem was the intermolecular alkylation with excess 1 at higher temperatures. It was overcome by employing high dilution method. Thus, after adding ethyl 8-iodo-2-octenoate (13) to 1 in THF at -78 °C, cooled THF

was added to adjust the concentration to 0.005M, and the mixture was allowed to react at 0 °C for 2 h. t-Butyl 2-ethoxycarbonyl-1-cycloheptanepropionate (14) was isolated in 58% yield as a 3.5:1 mixture of trans- and cis-isomer. Enolate 9 gave a 1:1 mixture of two diastereomers 15 (60% yield), tentatively assigned as epimers of the chiral center at the side chain. Presumably, epimerization occurred during the relatively slow cyclization process at higher temperatures (Scheme 5).



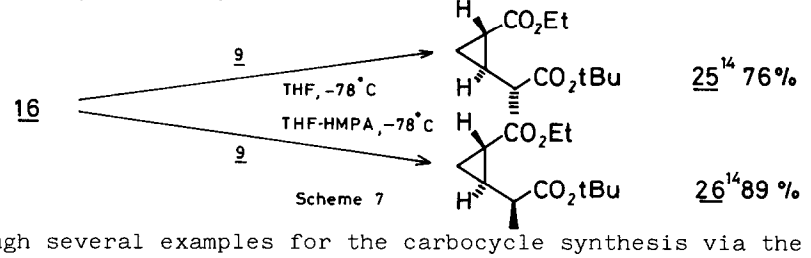
Scheme 5

Cyclopropane synthesis using 4-bromocrotonate (16) with various nucleophiles including ester enolates is well-known.[5] The stereochemistry, however, was less discussed. Thus, enolate 1 was treated with 16 in THF at -78 °C, and the expected cyclopropane 17 was obtained highly selectively. In contrast with five and six-membered cyclization, cyclopropanation occurred without potassium t-butoxide (Scheme 6). The trans-configuration was determined by ^{1}H-NMR spectroscopy. One of the ring protons appeared at δ 0.78 (ddd, J=4,6.5,8.5Hz).[6] The



Scheme 6

addition of 9 under appropriate conditions mentioned above also gave a single isomer concerning three asymmetric centers in series (Scheme 7).



Scheme 7

Although several examples for the carbocycle synthesis via the Michael induced alkylation of unsaturates esters are reported,[5, 7, 8, 9] the present method has several synthetic charasteristics: 1) Two ester moieties with different reactivities are formed, and a further transformation of this group is possible. 2) A high stereoselectivity is attained concerning three chiral centers, and the extracyclic asymmetric centers with either configuration could be prepared —— an serious problem encountered in the synthesis of steroids and several terpenoids.[10] Synthesis of natural products employing this methodology is now in progress.

References

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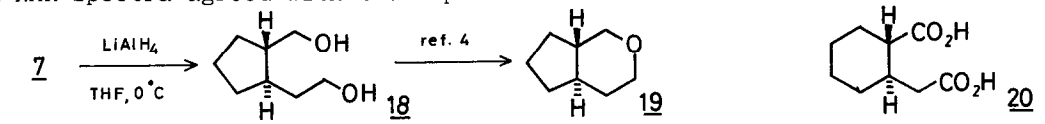
2 The ^{13}C-NMR chemical shifts of 3-methyl group of 2,3-dimethylglutarates are observed at δ 17.0±0.2 for erythro-isomers and δ 16.0±0.1 for threo-isomers in $CDCl_3$.

3 Cyclopentanepropionate 7 was converted to diol 18 with $LiAlH_4$ in THF at 0 °C Bisurethane mp 97 °C (lit.[11] 103 °C). Cf. Cis-isomer; mp 118 °C.[11] Diol 18 was further transformed to tetrahydropyran 19 by the method we have reported.[4] ^{1}H-NMR spectra agreed with the reported value.[11]



Cyclohexanepropionate 8 was treated with refluxing 2N HCl for 2 h to give diacid 20; mp 161 °C (lit.[12] 160 °C). Cf. Cis-isomer; mp 148 °C.[13]

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10 For example; P. A. Bartlett, Tetrahedron, 36, 2 (1980).

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14 The ^{13}C-NMR spectral data of several compounds in $CDCl_3$ are shown in δ. 21. 13.9, 14.2, 24.9, 27.7, 29.4, 30.9, 43.7, 45.5, 47.2, 59.8, 79.6, 174.5, 175.9. 22. 13.9, 15.8, 24.9, 27.8, 30.2, 31.1, 44.4, 46.4, 47.6, 59.8, 79.6, 174.4, 176.0. 23. 9.6, 13.9, 25.1, 25.3, 27.8, 29.8, 40.8, 41.4, 46.5, 59.7, 79.4, 174.1, 174.7. 24. 14.2, 15.3, 25.7, 25.8, 26.0, 28.1, 30.9, 42.0, 42.8, 47.6, 59.8, 79.9, 173.9, 175.6. 25. 13.8, 14.2, 16.0, 19.4, 25.7, 27.9, 43.8, 60.2, 80.2, 173.5, 174.0. 26. 14.1, 16.1, 18.9, 25.4, 27.9, 43.6, 60.2, 80.2, 173.6, 173.8.

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