A Stereoselective Route to Vicinally Substituted Cyclopentane- and Cyclobutane-carboxylates

Deukjoon Kim,[a]* Yoo Mi Jang,[a] In O Kim,[b] and Sang Woo Park[b]

[a] *College of Pharmacy, Seoul National University, San 56-1, Shinrim-Dong, Kwanak-Ku, Seoul 151, Korea*
[b] *Division of Chemistry, Korea Advanced Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul, Korea*

Intramolecular alkylation of the enolates derived from the esters (**3**) and (**7**) stereoselectively afforded the cyclopentanecarboxylate (**4**) and the cyclobutanecarboxylate (**8**), respectively; compound (**8**) is a potential intermediate for the synthesis of (±)-fragranol (**10**).

Vicinally substituted cycloalkanecarboxylates (**1a—c**) are frequently employed as intermediates in the synthesis of natural products. We recently reported a highly stereoselective, efficient route to *cis*-1,2-dialkylcyclohexanecarboxylate systems (**1a**) by intramolecular ester enolate alkylation.[1] The limited number of highly stereoselective methods for construction of *cis*-1,2-dialkylcyclopentane- and cyclobutanecarboxylates (**1b,c**), coupled with the significance of these compounds in natural product synthesis, prompted us to extend our alkylation methodology to smaller rings.[2]

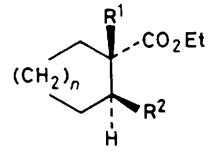
The intramolecular alkylation substrate (**3**) for the synthesis of a five-membered ring system was prepared from the known lactol (**2**)[3] in a straightforward six-step sequence in 56% overall yield as summarized in Scheme 1.

Upon treatment with lithium di-isopropylamide in tetrahydrofuran at −78 °C for 1 h, compound (**3**) underwent smooth cyclization to furnish a 92 : 8 mixture of cyclopentanecarboxylates (**4**) and (**5**) in 45% unoptimized yield.† Use of potassium hexamethyldisilazide as base gave a less satisfactory 88 : 12 mixture in comparable yield. Stereochemical assignments of (**4**) and (**5**) were based upon the differences in the chemical shifts (see structures) of the quaternary methyl and ethyl ester methylene groups in their 200 MHz ^{1}H n.m.r. spectra (*vide infra*) due to the shielding effect of the adjacent vinyl group.[4]

Stereoselective construction of four-membered ring systems is illustrated in the context of synthesis of cyclobutanecarboxylates (**8**) and (**9**), potential intermediates for (±)-fragranol (**10**) and (±)-grandisol (**11**).[5]‡ The key cyclization substrate (**7**) was prepared from the known homoallylic alcohol (**6**)[6] by a conventional five-step sequence (Scheme 2).

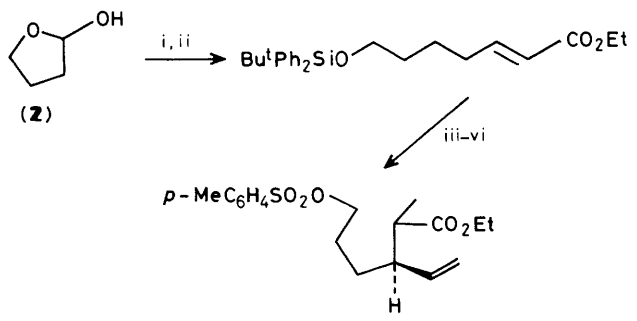
Alkylative cyclization of the tosylate (**7**) with lithium di-isopropylamide in THF at −78 °C to room temperature gave a 97 : 3 mixture of cyclobutanecarboxylates (**8**) and (**9**) in 45% yield.† The corresponding potassium enolate generated by treatment of (**7**) with potassium hexamethyldisilazide afforded a 95 : 5 mixture of (**8**) and (**9**) in 65% yield. The chemical shift values of the quaternary methyl and methine protons in (**8**) and (**9**) were again diagnostic for the stereochemistry.†

The observed high stereoselectivity in these alkylations can best be rationalized by considering that the reactions proceed *via* the more stable 'eclipsed' transition state geometry (**12**), rather than the 'bisected' one (**13**).[7] It should be noted that the presumably less aggregated and more reactive potassium enolate gave slightly inferior stereoselectivity compared to the corresponding lithium enolate in all cases (n = 2, 1, 0) studied



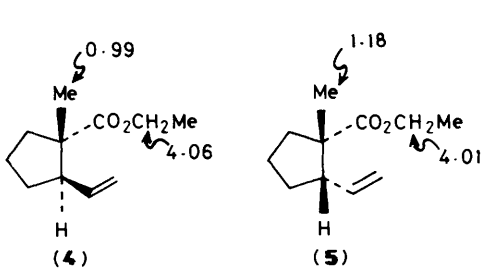
(**1**)

a; n = 2
b; n = 1
c; n = 0



(**3**)

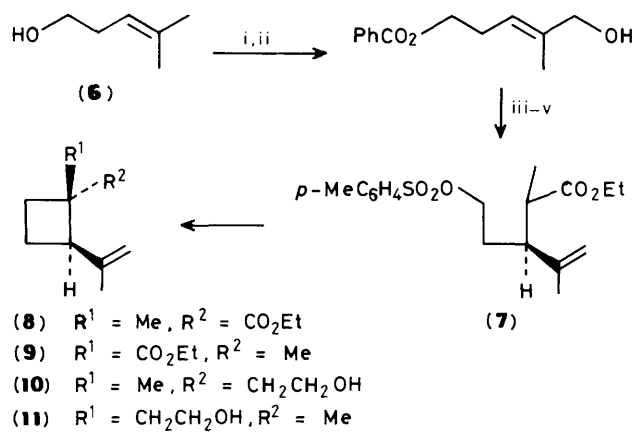
Scheme 1. *Reagents*: i, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux, 2 h; ii, Bu^tPh_2SiCl, imidazole, dimethylformamide, room temp., 2 h (93% for 2 steps); iii, Bu^i_2AlH, toluene, room temp., 4 h (96%); iv, $MeCH_2C(OEt)_3$, phenol, 165 °C, 4 h (90%); v, Bu^n_4NF, tetrahydrofuran (THF), room temp., 2 h (85%); vi, *p*-$MeC_6H_4SO_2Cl$, 4-*N*,*N*-dimethylaminopyridine, CH_2Cl_2. room temp., 2 h (82%).



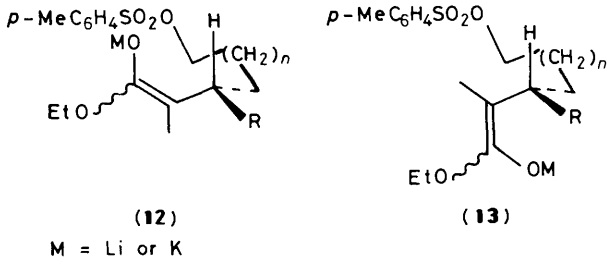
(**4**) (**5**)

† The ratio of stereoisomers was determined by capillary g.c. analysis (0.2 mm i.d. × 50 m; CBP-1). The volatility of the products might be responsible for the moderate isolated yields. All new compounds gave satisfactory spectral data. Compound (**4**): i.r. (film) ν 1740 cm^{-1}; ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 5.71 (m, 1H), 4.98 (m, 1H), 4.92 (m, 1H), 4.06 (q, *J* 7 Hz, 2H), 2.82 (m, 1H), 2.30—1.40 (m, 6H), 1.17 (t, *J* 7 Hz, 3H), 0.99 (s, 3H); ^{13}C n.m.r. (20.15 MHz, $CDCl_3$) δ 177.69, 138.32, 115.43, 60.29, 52.10, 51.10, 38.20, 29.63, 22.43, 18.44, 14.25. (**8**): i.r. (film) ν 1740 cm^{-1}; ^{1}H n.m.r. (80 MHz, $CDCl_3$) δ 4.90 (m, 1H), 4.69 (br. s, 1H), 4.16 (q, *J* 7 Hz, 2H), 3.23 (t, *J* 7 Hz, 1H), 2.45—1.78 (m, 4H), 1.65 (s, 3H), 1.26 (t, *J* 7 Hz, 3H), 1.16 (s, 3H). (**9**): An authentic sample was prepared from the corresponding acid[5] by treatment with Triton B and EtI in THF at room temperature: i.r. (film) ν 1740 cm^{-1}; ^{1}H n.m.r. (80 MHz, $CDCl_3$) δ 4.78 (br. s, 1H), 4.67 (br. s, 1H), 4.10 (q, *J* 7 Hz, 2H), 2.82 (t, *J* 7 Hz, 1H), 2.40—1.83 (m, 4H), 1.71 (s, 3H), 1.46 (s, 3H), 1.23 (t, *J* 7 Hz, 3H).

‡ We believe this intramolecular ester enolate alkylation scheme could be readily modified for the stereoselective synthesis of the grandisol skeleton.



Scheme 2. *Reagents*: i, PhCOCl, pyridine, room temp., 12 h (90%); ii, SeO_2, EtOH, reflux, 3 h, then $NaBH_4$, 0 °C, 2 h (62%); iii, $MeCH_2C(OEt)_3$, phenol, 165 °C, 8 h (85%); iv, Triton B, THF, reflux, 1 h, then EtI, reflux, 30 min (70%); v, *p*-$MeC_6H_4SO_2Cl$, 4-*N*,*N*-dimethylaminopyridine, CH_2Cl_2, room temp., 2 h (81%).



in our laboratory,[1] but afforded better yields, especially in the sterically demanding cases.

In summary, we have developed a stereoselective method for the construction of vicinally disubstituted cyclopentane- and cyclobutane-carboxylates which has wide ranging potential in organic synthesis along with our previously disclosed work on intramolecular alkylations to form six-membered rings.[1]

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