Folding strain stereocontrol in cyclohexane ring formation by means of an intramolecular ester enolate alkylation reaction

Takashi Tokoroyama and Hisashi Kusaka

Abstract: Diastereoselectivity in the cyclization of ethyl 7-bromo-2-methylheptanoates with an additional substituent at various positions in the chain, by LDA treatment, was investigated in connection with the concept of folding strain stereocontrol. Cyclization of 3-, 4-, and 6-methyl-substituted substrates revealed high selectivity, which demonstrates the prevalence of folding strain stereocontrol and the usefulness of this approach for stereoselective ring construction. In particular, reactions of the latter two substrates resulted in the stereodivergent preparation of diastereomeric 1,3-dimethylcyclohexanecarboxylates. In the case of the 5-methyl-substituted substrate, the selectivity of ring closure was only moderate. ^{1}H and ^{13}C NMR spectroscopic data were useful for determining the conformation of 1-methylcyclohexanecarboxylate derivatives. The origin of the diastereoselectivity was examined through the qualitative comparison of the strain in the diastereomeric folding in the transition state. Various factors that might affect stereoselectivity were examined in the cyclization of 5-substituted substrates to better understand this concept. As predicted, the selectivity increased as the substituent became bulkier: Ph < Me ≈ Et < i-Pr < *t*-Bu. The effects of other factors — solvent, base counter cation, and leaving group — on selectivity agree with results predicted from the reactivity–selectivity relationship.

Key words: folding strain stereocontrol; diastereoselectivity in ring-closure reaction; remote asymmetric induction; ethyl 2-methylcyclohexanecarboxylate derivatives, ^{1}H and ^{13}C NMR; stereoselective synthesis of substituted cyclohexane derivatives.

Résumé : Dans le cadre de travaux sur le concept du stéréocontrôle par le plissement des chaînes, on a étudié la diastéréosélectivité de la cyclisation, sous l'influence du LDA, de 7-bromo-2-méthylheptanoates d'éthyle portant un substituant additionnel dans diverses positions. Les cyclisations des substrats substitués par des groupes méthyles en positions 3, 4 ou 6 se produisent avec une grande sélectivité; ceci met en évidence la prévalence du stéréocontrôle par le plissement de la chaîne et démontre l'utilité de cette approche pour la formation stéréosélective de cycles. Ceci est particulièrement vrai avec les deux derniers substrats qui conduisent à la préparation stéréoconvergente des 1,3-diméthylcyclohexanecarboxylates diastéréomères. Dans le cas du substrat portant un groupe méthyle en position 5, la sélectivité de la formation du cycle n'est que modérée. Les données de la spectroscopie RMN du ^{1}H et du ^{13}C se sont avérées utiles pour la détermination de la conformation des dérivés 1-méthylcyclohexanecarboxylates. On a étudié l'origine de la diastéréosélectivité par le biais d'une comparaison qualitative de la tension dans le plissement diastéréomère dans l'état de transition. Dans le but de mieux comprendre ce concept, on a examiné divers facteurs pouvant affecter la stéréosélectivité lors de la cyclisation de substrats substitués en position 5. Tel qu'on pouvait le prévoir, la sélectivité augmente avec une augmentation de l'encombrement du substituant : Ph < Me ≈ Et < i-Pr < *t*-Bu. Les effets des autres facteurs — solvant, contre-ion basique et le groupe partant — sur la sélectivité sont en accord avec les résultats prédits sur la base de la relation réactivité–sélectivité.

Mots clés : stéréocontrôle par le plissement de la chaîne; diastéréosélectivité lors de réactions de cyclisation; induction asymétrique à distance; RMN ^{1}H et ^{13}C de dérivés du 2-méthylcyclohexanecarboxylate d'éthyle; synthèse stéréosélective de dérivés du cyclohexane substitué.

[Traduit par la rédaction]

Introduction

Diastereoselective cyclization is an efficient approach for the synthesis of ring compounds, with stereoselective installation of substituents on the ring (1). For this reason, cycloaddition reactions, such as the Diels–Alder reaction, are considered a powerful synthetic tool (2). In contrast, diastereocontrol in a simple ring-closure reaction has attracted far less attention. In connection with the stereoselective synthesis of natural products (3), we previously found that the cyclization of 2-(3′,4′-dimethyl-6′-trimethylsilylhex-4′-enyl)cyclohex-2-enone (**1**) proceeded with twofold stereocontrol to give the decalone derivative (**2**) as a single diastereomer (Scheme 1) (4). One of the stereocontrol factors involved the diastereofacial selection based on the conformational preference of the 3′-methyl group with respect to the diastereomeric folding of the acyclic chain in the transition state. We have pointed out the general utility

Received March 14, 1995.[1]

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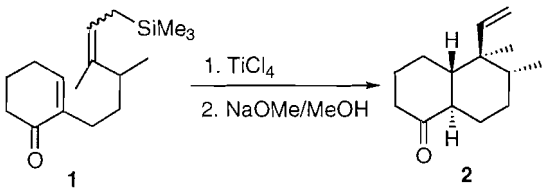
Scheme 1.



of this type of stereoselection for the diastereoselective construction of ring compounds in terms of folding strain stereocontrol (5–7).

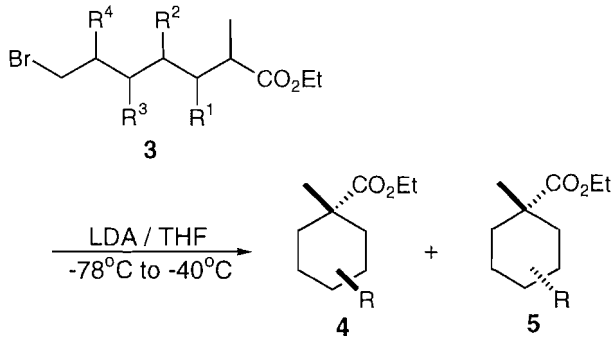
For the intermolecular reaction of acyclic molecules, diastereoselection is generally effective only for 1,2-asymmetric induction without the intervention of chelation or other special conditions. However, for intramolecular reactions, the relative steric strain in the diastereomeric folding of the chain may greatly affect the stereoselectivity, and thus the asymmetric induction, more than a 1,3-relationship to the stereogenic center, could be effective in the folding strain stereocontrol. We believe that the diastereofacial selectivity in a ring-closure reaction is determined by the difference in the total strain energy ($\Delta(SE)_{AB}^{*}$), between the diastereomeric transition states (A,B) and that, even if the stereocenter in the chain is remote from the bond-forming atom, the energy difference could be great enough for the diastereoselection to be effective. Moreover, the design of a stereoselective cyclization may be possible by estimating the strain energy involved. Just as diastereodifferentiation in some acyclic stereocontrols is due to the energy difference between diastereomeric cyclic transition states (e.g., aldol reaction and the Claisen rearrangement) (8), the relative energy of diastereomeric foldings in the transition state determines diastereoselection in the ring-closure reaction. Particularly in carbocyclic six-membered ring formation, the difference in conformational energy between the transition states could be more distinct than that in systems involving many sp^2 carbon atoms and hetero atoms, and a better diastereoselectivity would be reasonably expected. Thus, a high possibility of remote diastereocontrol could be anticipated in carbocyclic ring formation. Although several examples of stereocontrols of this type can be found in the literature, a systematic investigation to demonstrate the underlying concept is lacking (for notable examples, see ref. 9). To further test the feasibility of our concept, we investigated diastereofacial selectivity in the cyclization of ethyl 7-bromo-2-methylheptanoates **3** with a substituent at various positions in the chain to diastereomeric cyclohexanecarboxylates **4** and **5** via an intramolecular ester enolate alkylation reaction (Scheme 2). Kim et al. have used cyclization reactions of this type for the stereoselective synthesis of cyclic natural products (*9f–9n*).

Results and discussion

Synthesis of cyclization substrates

Ethyl 7-bromo-2,3-dimethylheptanoate (**11**) was synthesized by the alkylation of acetoacetate dianion with 3-benzyloxypropyl bromide (**7**) and subsequent successive introduction of methyl groups at the 3 and 2 positions as shown in Scheme 3. To introduce the 3-methyl group, the combination of Nozaki and Weiler methods (10) was used and the resultant trisubstituted olefin was catalytically hydrogenated.

Scheme 2.



Ethyl 7-bromo-2,4-dimethylheptanoate (**15**) was synthesized by homologation of 2-methyl-δ-valerolactone (**12**) using in situ reduction and the Horner–Emmons reaction (11) (Scheme 4). The synthesis of *ethyl 7-bromo-2,5-dimethylheptanoate* (**19**) was achieved in the same way by starting from 3-methyl-δ-valerolactone (**17**) obtained by the NaBH4 reduction (12) of 3-methylglutaric anhydride (**16**) (Scheme 5). Substrates **25** and **26**, which have a 5-ethyl and a 5-isopropyl group, respectively, were synthesized by the introduction of the alkyl groups through the copper-catalyzed conjugate addition (13) of Grignard reagents to 2-penten-5-olide (**20**) and the subsequent transformations were similar to those described above (Scheme 5). To synthesize the *5-phenyl substrate* **30** the requisite 3-phenyl-δ-valerolactone (**28**) was prepared by the $NaBH_4$ reduction of 3-phenylglutaric anhydride (**27**). To synthesize the 5-*tert*-butyl substrate **35**, since the anhydride corresponding to **27** could not be obtained by the Michael reaction of methyl 4,4-dimethyl-2-pentenoate with dimethyl malonate, the other method shown in Scheme 6 was used. *Ethyl 7-bromo-2,6-dimethylheptanoate* (**39**) was synthesized by the homologation of 4-methyl-δ-valerolactone (**37**) (Scheme 7). The substrates **11**, **15**, **19**, **25**, **26**, **30**, **35**, and **39** were all obtained as a mixture of diastereomers, as seen distinctly from their ^{13}C NMR spectra.

Cyclization and stereochemical assignment of the diastereomeric products

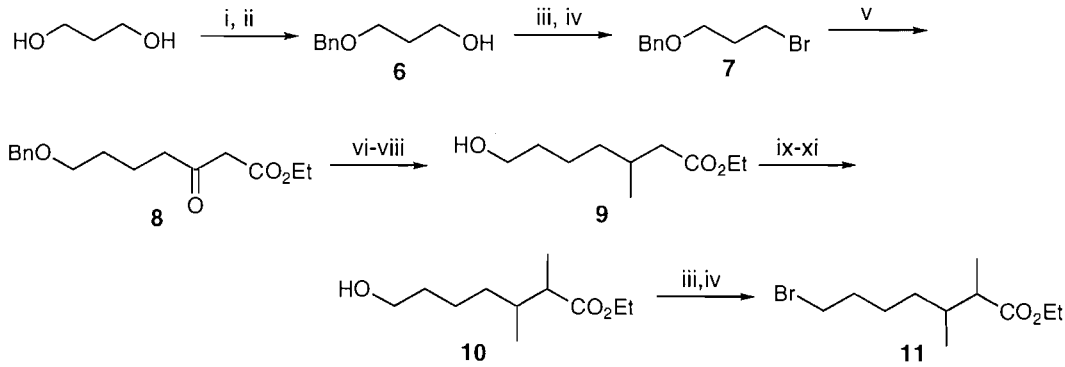
Cyclization was performed in THF using three equivalents of LDA at −78°C for 1 h, and moderate to good yields of the cyclization products were generally obtained under these conditions. The isomer ratios were determined by capillary GPC. Stereochemical assignment of the diastereomeric products was carried out effectively by the analysis of 400 MHz ^1H and ^{13}C NMR spectra with reference to those reported in the literature, when available. The results are shown in Tables 1–5.

Ethyl trans-*1,2-dimethylcyclohexanecarboxylate (40)*[3]

The ^1H NMR spectra of the major product in the cyclization of ethyl 7-bromo-2,3-dimethylheptanoate (**11**) agree well with the data reported for the methyl ester corresponding to the *trans* compound **40**, except with regard to the signal due to the

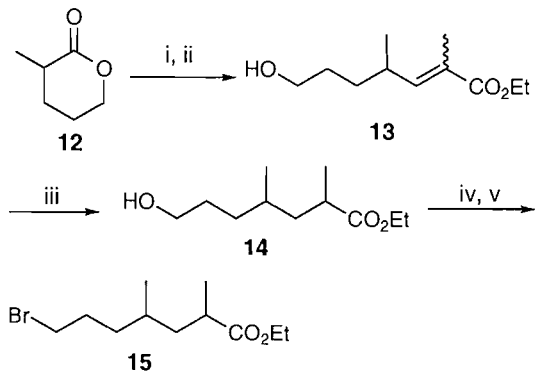
[3] Throughout this paper, the *cis–trans* notation for the relative configuration of substituted cyclohexanecarboxylate derivatives refers to the ester groups.

Scheme 3.



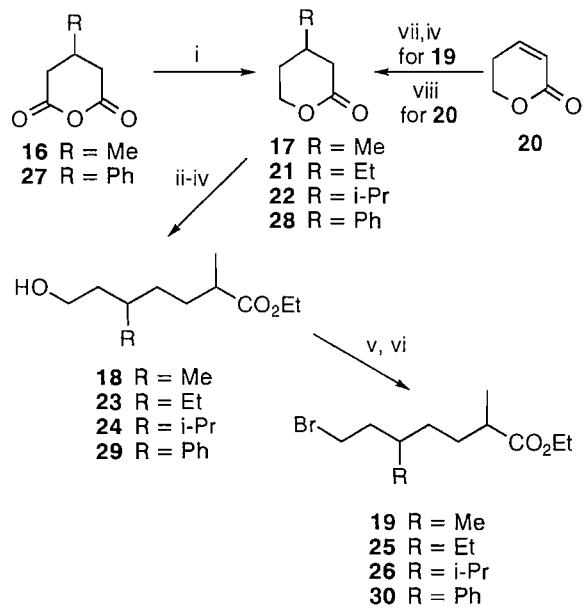
(i) PhCHO, TsOH; (ii) $LiAlH_4$, $AlCl_3$; (iii) MsCl, Et_3N; (iv) LiBr; (v) ethyl acetoacetate dianion; (vi) $(EtO)_2P(O)Cl$, NaH; (vii) $Pd(PPh_3)_2Cl_2$, Me_3Al; (viii) H_2, Pd-C; (ix) MOMCl, $i\text{-}Pr_2NEt$; (x) MeI, NaH; (xi) 6 N HCl

Scheme 4.



(i) DIBAL; (ii) $(EtO)_2P(O)CHMeCO_2Et$, BuLi; (iii) H_2, Pd-C; (iv) MsCl, Et_3N; (v) LiBr

Scheme 5.



(i) $NaBH_4$, THF; (ii) DIBAH; (iii) $(EtO)_2P(O)CHMeCO_2Et$, BuLi; (iv) H_2, Pd-C; (v) MsCl, Et_3N; (vi) LiBr; (vii) CH_2=CHMgBr, CuI; (viii) $Me_2CHMgBr$, CuI

ester groups (14, 15). When the ^1H NMR spectra of **40** was analyzed using a COSY experiment, the coupling constants between the resonances of the 2-H proton and 3-methylene protons were found to be 3.1 and 10.5 Hz. Therefore, the 2-H proton was concluded to be axial, and the 2-methyl group was considered to assume an equatorial conformation. Moreover, the appearance of the 2-H proton signal at a rather deshielded position (δ 2.01) indicated that the ethoxycarbonyl group is in an equatorial conformation (vide infra).

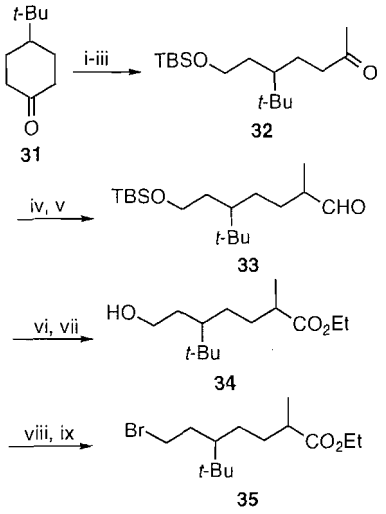
Ethyl cis- *and* trans-*1,3-dimethylcyclohexanecarboxylates (42 and 43)*

The diastereomers **42** and **43** were obtained as the major products, respectively, in the cyclization of 2,4- and 2,6-dimethyl-7-bromoheptanoic acid esters **15** and **39**. Comparison of the ^1H NMR data with those reported previously (15, 16) suggested that they represented *cis* and *trans* compounds, respectively. The difference between **42** and **43** was more distinct in the ^{13}C NMR spectra in which the signals due to the tertiary methyl groups were observed higher upfield in the former (δ 20.5) than in the latter (δ 28.7). This fact indicates that the former methyl group is axial and the latter is equatorial. Furthermore, in the ^1H NMR spectra, the *trans* ester **43** exhibited signals due to the equatorial C-2 and C-6 protons at deshielded positions (δ 2.13 and 2.16, respectively), while those of the *cis* ester **42** appeared in a normal range, with the ethoxycarbonyl group in **42** and **43** in equatorial and axial orientation, respectively. The ^{13}C resonances of the secondary methyl groups in **42** and **43** were located at a similar field (δ 22.8 and 22.4).

Ethyl trans- *and* cis-*1,4-dimethylcyclohexanecarboxylates (44 and 45)*

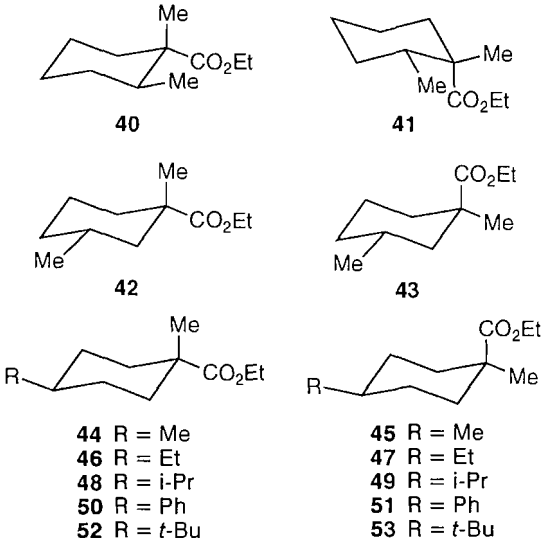
The mixture of diastereomers obtained by the cyclization of **19** was separated by flash chromatography, and their conformation was studied by ^1H and ^{13}C NMR spectroscopy. In ^{13}C NMR spectra of the major and minor products, the signals due to tertiary and secondary methyl groups were observed at δ 20.8, 22.7 and δ 28.3, 22.4, respectively. Thus, the former was

Scheme 6.



(i) MCPBA; (ii) MeLi; (iii) TBDMSCl, imidazole; (iv) $Ph_3P{=}CHOMe$; (v) $HClO_4$, H_2O; (vi) $KMnO_4$, NaH_2PO_4; (vii) EtOH, TsOH; (viii) MsCl. Et_3N; (ix) LiBr.

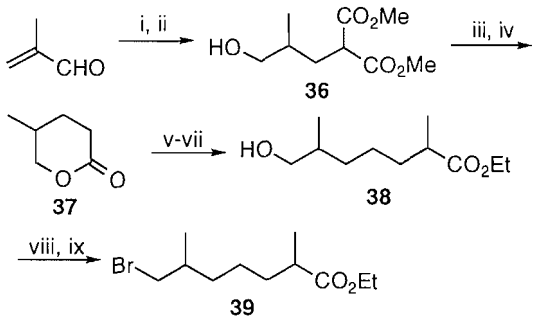
considered to have the *trans* structure (**44**) and the latter the *cis* structure (**45**). This assignment was consistent with the difference in the ^1H NMR spectra for both products. The signals of the 2-H_{eq} (= 6-H_{eq}) and 3-H_{ax} (= 5-H_{ax}) protons for **45** appeared at a deshielded (δ 2.17 vs. 1.58 for **44**) and shielded position (δ 0.96 vs. 1.69 for **44**), respectively, which was ascribed to the axial conformation of an ethoxycarbonyl group in **45**.



Ethyl trans- *and* cis-*4-ethyl-, 4-isopropyl-, 4-phenyl-, or 4-tert-butyl-1-methylcyclohexanecarboxylates (46–53)*

In these compounds C-4 substituents are believed to lock the conformation, in which they are disposed equatorially, even more strictly than in the 4-methyl analogs above. Thus, the configurations of the diastereomeric products were most readily assigned by comparing the chemical shift values of the signals due to 1-methyl groups in ^{13}C NMR spectra; i.e., the compound with the larger δ value was considered to be *cis* and the one with the smaller δ value *trans*. Additional support for these assignments was obtained by analyzing ^1H NMR spectra, as with the 4-methyl analog described above.[4]

Scheme 7.



(i) $CH_2(CO_2Me)_2$, Et_3N; (ii) $NaBH_4$; (iii) KOH; (iv) H_2SO_4; (v) DIBAH; (vi) $(EtO)_2P(O)CHMeCO_2Et$, BuLi; (vii) H_2, Pd-C; (viii) MsCl, Et_3N; (ix) LiBr.

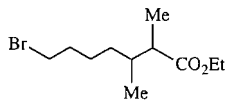
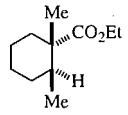
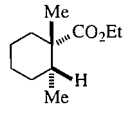
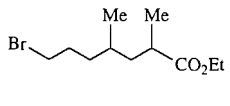
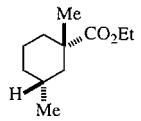
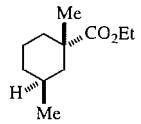
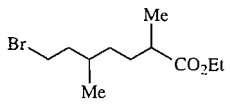
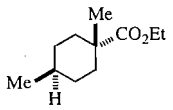
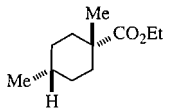
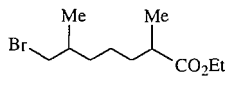
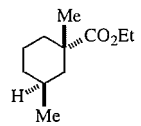
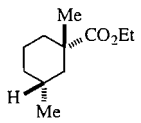
Diastereoselectivity in the cyclization of ethyl 7-bromo-2-methylheptanoates with a methyl substituent at various positions in the chain

The ratios of the diastereomeric products observed in the cyclization of substrate **3** with a methyl group at various positions are summarized in Table 1. The reaction shows generally good selectivity, except in the case of 5-methyl-substituted substrate **19**. These results indicate that the remote stereocontrol in a simple ring-closure reaction would have greater potential than is generally thought (1) for the stereoselective synthesis of cyclic compounds, even though the bulkiness of the substituent and the type of the reaction concerned must be taken into account. In the following discussion, the relationship between the degree of diastereoselectivity and the energy difference of the diastereomeric transition states estimated qualitatively from the folding strains is addressed separately for the individual substrates. We have made two assumptions regarding the conformation of the transition state for the sake of simplification.[5] First, we assume that the chair conformation is decidedly preferred over the twist-boat conformation. Second, we assume that the eclipsed (skew) form **54** is favored over the bisected (*gauche*) form **55**, as has been pointed out also by D. Kim et al. (9*g*, 9*k*). The latter assumption is based on the generally accepted view regarding allylic systems, which is supported by the results of computational studies (17, 18). However, these studies have also revealed that the energy difference between the skew and *gauche* forms is much smaller in the model enolate system **56** than in the crotyl analog **57** (1.7 vs. 3.4 kcal/mol) (17). If the presence of the C-2

[4] The ^1H NMR spectral data for the *trans* and *cis* methyl esters corresponding to **52** and **53** were given in ref. 15, but these could not be used to distinguish between the diastereomeric products.

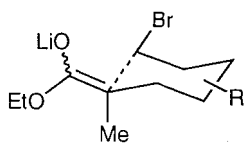
[5] The cyclization is considered to proceed mainly via *E*-enolates (19). The effect of enolate geometry on this issue is unknown, though it is not believed to be very important. A cyclization experiment with the substrates with bulkier ester alkyl groups might be informative in this regard.

Table 1. Remote diastereocontrol in the cyclization of ethyl 7-bromo-2-methylheptanoates with a methyl group at various positions in the chain.[a]

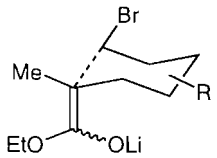
Entry	Subrates	Cyclization products		Diastereomeric ratio (yield)
1	 **11**	 **40**	 **41**	**40** : **41** = 96 : 4 (78%)
2	 **15**	 **42**	 **43**	**42** : **43** = >99 : 4 (83%)
3	 **19**	 **44**	 **45**	**44** : **45** = 79 : 21 (66%)
4	 **39**	 **43**	 **42**	**43** : **42** = 93 : 7 (53%)

[a]The reactions were conducted with 3 equivalents of LDA in THF at −78°C.

methyl group is taken into account, the energy difference between the transition states (TS) **54** and **55** could be considerably less than the former value, since the *gauche* interaction between the 2-methyl group and the C-3—C-4 bond might destabilize TS **54**.



54



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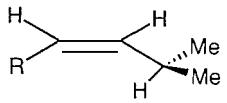
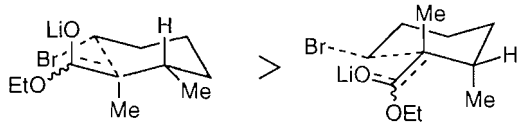


56 R = OMe
57 R = Me

*Cyclization of ethyl 7-bromo-2,3-dimethylheptanoate (**11**)*
In this cyclization, a stereogenic center exists next to the bond-forming carbon atom of an allylic system. Our dually stereocontrolled cyclization reaction mentioned at the outset (Scheme 1) involves this type of stereocontrol. Most of the stereocontrols used by Kim et al. (9) also belong to this category. They have reported an overall selectivity of 98:2 in the cyclization of substrate analogous to **11** (2-butyl and 7-tosyloxy groups instead of 2-methyl and 7-bromo, respectively) (9*f*). The major factors that affect selectivity include the $A^{1,3}$ strain (18, 20) and the additional *gauche* repulsion (quasi-axial vs. quasi-equatorial conformations of the 3-methyl group), both of which make TS **59** unfavorable and lead to the *cis* product through TS **58**.[6] The latter effect is inherent in the



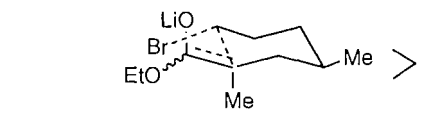
58 > **59**

ring-closure reaction of a carbon chain and should not be neglected (~ 1.8 kcal). In contrast to the models (21, 22) postulated to explain the diastereofacial selectivity in the intermolecular reaction of ester enolates with a β-stereogenic center, where the stereoelectronic effect plays an important role, the steric constraint resulting from the folding of the chain is an additional significant factor in determining the selectivity in the ring-forming reaction. Selectivity in the cyclization of substrates with a substituent remote from the atom on which the bonding occurs largely depends on the extent of the strain energy involved in the chain folding (1,*n*-asymmetric induction, $n \geq 3$).

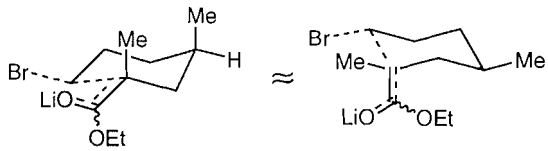
*Cyclization of 7-bromo-2,4-dimethylheptanoate (**15**)*
The diastereoselectivity for the *cis* product **42** was excellent, and formation of the *trans* product **43** was not detected. TS **61**,

[6] The sign of the inequality between formulas for the transition state conformations denotes the energy (or kinetic) preference.

which leads to the *trans* product **43**, is destabilized relative to *cis*-TS **60** by *gauche* repulsion (~1.8 kcal/mol) and 1,3-diaxial dimethyl interaction (3.7 kcal/mol) (23, 24). This energy difference (<5.5 kcal/mol)[7] is sufficient to explain the selectivity of greater than 99%. Incidentally, the *gauche* transition state **62**, which has no destabilization due to severe 1,3-diaxial dimethyl repulsion, must have a strain energy lower than that of **61**, but higher than that of **60**.



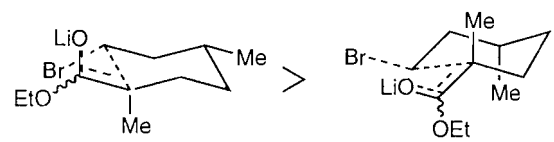
60



61 **62**

Cyclization of ethyl 7-bromo-2,5-dimethylheptanoate (19)

In this cyclization, formation of the *trans* product **44** was preferred to that of the *cis* product **45** by a ratio of 79:21, which corresponds roughly to the energy difference of 0.8 kcal/mol between the diastereomeric transition states. This selectivity is lower than that expected from the conformational energy difference between **63** and **64** (quasi-equatorial vs. quasi-axial methyl groups, ~1.8 kcal/mol). One of the bonds (C-5—C-6) *gauche* to the axial methyl group in TS **64** located at an end is less sterically constrained, provided that the C-1—C-6 bond remains loose and that the ester enolate alkylation reaction involves an early transition state, as generally postulated (19). This situation would account for the lower selectivity.

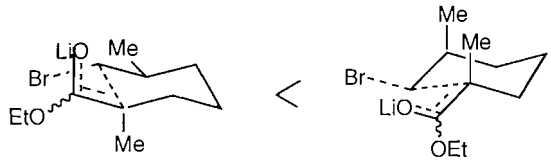


63 **64**

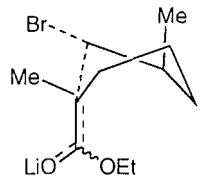
Cyclization of ethyl 7-bromo-2,6-dimethylheptanoate (39)

In this case, the *trans* product **43** was formed predominantly rather than the *cis* isomer **42**, which indicates that TS **66** is preferred to **65**. This fact might be explained by the presence of a severe torsional strain between the 6-methyl and the bromine bonds in TS **65**, which are nearly synperiplanar. While the diastereomeric TS **66** appears to suffer from 1,3-diaxial dimethyl interaction (~3.7 kcal/mol) (23, 24), twist-boat TS **66a** is unlikely since it is doubly disadvantaged (twist-boat form and the *gauche* form). Also, the 1,3-diaxial dimethyl interaction in TS **66** might not be as strong as in a normal cyclohexane ring since the loose C-1—C-6 bond intervenes between the two carbon atoms bearing methyl groups, which differs from the situation in TS **61**. The strong dependence of van der Waals repulsion on the distance between the atoms is well known (25).

[7] The energy difference between the transition states should be less than that estimated for the cyclohexane products, due to the looseness of the emerging bond.



65 **66**



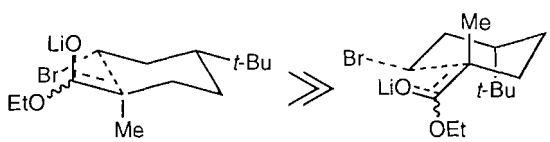
66a

Factors influencing diastereoselectivity

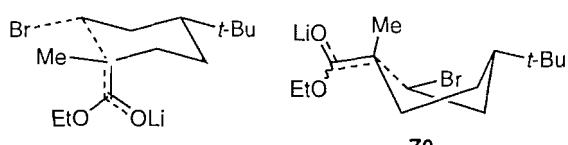
Various parameters that may affect the diastereofacial selectivity, including the size of 5-substituents, were investigated to better understand the parameters governing the cyclization of ethyl 7-bromo-2,5-dimethylheptanoate (**19**), which shows only moderate stereoselectivity.

Relationship between diastereoselectivity and bulkiness of the substituent in the chain

The steric bulkiness of the substituents is believed to greatly affect the energy difference between the diastereomeric transition states, and hence the diastereoselectivity. This subject was investigated in the cyclization of substrate **3**, which carries substituents of various sizes at the 5-position. The results are shown in Table 2 with the relevant conformational free energy (*A*-values) (ref. 24, pp. 433–436, and ref. 26). Generally, selectivity was enhanced as the bulkiness of the 5-substituents increased, as anticipated. However, two points should be mentioned. First, a change in the 5-substituent from methyl to phenyl resulted in a decrease in selectivity, which was contrary to the result predicted from the *A*-values. This result is supported by the fact that in the equilibrium of 1-methyl-1-phenylcyclohexane conformers, the methyl group prefers the equatorial position by 0.3 kcal/mol (27, 28; see also ref. 12). A computational study on a simple allylic system (17) also showed that a phenyl group can be less effective than a methyl group in providing a conformational lock, depending on its disposition. Second, the diastereoselectivity observed for the 5-*tert*-butyl substrate **35** was not as high as expected, considering the ability of the *tert*-butyl group to lock the cyclohexane conformation. This result might indicate the intervention of a *gauche* TS **69** or a twist-boat TS **70** rather than a chair TS **68**, which would definitely be energetically unfavorable.

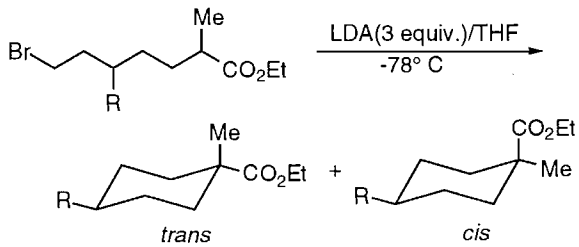


67 **68**



69 **70**

Table 2. Effect of the bulkiness of the substituent on diastereoselectivity in the cyclization of 5-substituted 7-bromo-2-methylheptanoates.



Entry	Substrate R	Substrate No.	Diastereomeric yield (%)	Products ratio (*trans*/*cis*)	A-value (kcal/mol)
1	Me	**19**	66	**44/45** = 79:21	1.8
2	Et	**25**	89	**46/47** = 79:21	1.8
3	i-Pr	**26**	85	**48/49** = 86:14	2.1
4	Ph	**30**	80	**50/51** = 74:26	2.9
5	*t*-Bu	**35**	77	**52/53** = 89:11	>4.5

Table 3. Effect of the solvent on diastereoselectivity in the cyclization of ethyl 7-bromo-2,5-dimethylheptanoate.[a]

Entry	Solvent	Reaction temp. (°C)	Yield (%)	Product ratio *trans*/cis (**44/45**)
1	Et_2O	−20[b]	72.9	73:27
2	THF	−78	66.0	79:21
3	DME	−78	77.5	69:31
4	THF/HMPA[c]	−78	71.9	52:48

[a]The reaction was conducted using 2.5 molar equivalents of LDA.
[b]The reaction did not proceed to completion at −78°C.
[c]HMPA was used in 13.4 molar equivalents.

Effect of the solvent

The effect of the solvent on the diastereoselectivity was examined in the cyclization of the 5-methyl substrate **19** (Table 3). Excluding the reaction in diethyl ether (entry 1), which was conducted at an elevated temperature, selectivity decreased in the order THF > DME > THF/HMPA. This order parallels the well-known increase in enolate reactivity due to the greater dissociation of the enolate cation ion pair and ion aggregate (ref. 26, p. 428). Based on the reactivity–selectivity principle (29), the increase in reactivity should diminish selectivity.

Effect of base counter cation

Kim et al. reported for one of their cyclization reactions that the use of LDA as a base gave better selectivity than potassium hexamethyldisilazide (KHMDS), albeit in poorer yield (9*g*). The results of our investigation in this regard are shown in Table 4. In comparing entries 2 and 4, the selectivity is slightly higher in the reaction with lithium hexamethyldisilazide

Table 4. Effect of the base on diastereoselectivity in the cyclization of ethyl 7-bromo-2,5-dimethylheptanoate.

Entry	Base[a]	Reaction temp. (°C)	Yield (%)	Product ratio *trans*/cis (**44/45**)
1	LDA	−78	66.0	79:21
2	LHMDS	r.t.	72.0	73:27
3	KHMDS	−25	67.6	71:29
4	KHMDS	r.t.	75.0	69:31

[a]Three equivalents were used.

(LHMDS) than with KHMDS. This result is consistent with the trend predicted from the reactivity–selectivity relationship, since the degree of ion-pair dissociation is greater in potassium enolate than in lithium enolate and the former should be more reactive.

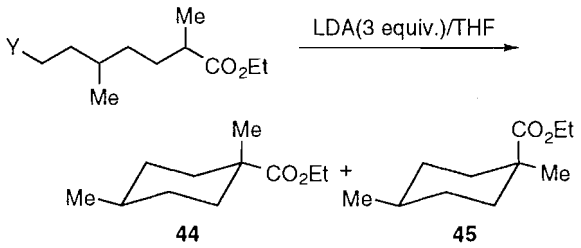
Leaving group effect

In the cyclization reactions described thus far, the observed selectivity is generally lower than that predicted from an estimation of the energy difference between the diastereomeric transition states based on the conformation of the product cyclohexane derivatives. This discrepancy may be largely attributed to the fact that the transition state involves a looser conformation than the product. The extent of the discrepancy should increase as the transition state occurs earlier in the reaction. This influence on selectivity is similar to Hammond–BEP behavior (29). Thus, we can predict that diastereoselectivity should decrease as the ease with which the leaving group dissociates increases. Our results are summarized in Table 5.

Conclusion

Diastereoselectivity in cyclohexane ring formation by the intramolecular ester enolate alkylation reaction has been investigated as a case study of the folding strain stereocontrol concept. In the cyclization of ethyl 7-bromo-2-methylheptanoates (**3**) with a methyl substituent at various positions in the chain under LDA treatment, good to excellent selectivities were obtained, with the exception of the case of 5-methyl, where the selectivity was only moderate. It would be valuable from a synthetic point of view that either of the diastereomeric 1,3-dimethylcyclohexanecarboxylates could be obtained stereoselectively merely by choosing the cyclization substrates. Thus, folding strain control could influence a ring-closure reaction to a greater extent than generally thought, and stereoselective ring construction using this approach would be useful. The direction of the selectivity can be explained by a qualitative consideration of the strain factors in the diastereomeric transition states. In this approach, the location of the bond formed relative to the stereogenic center is extremely important. Noteworthy results in this study include the difference in the degree of diastereoselectivity in cyclization between the 2,5-dimethyl and 2,6-dimethyl substrates **15** and **19**, and the unexpected preference for diastereomer **43** over **42** in the cyclization of substrate **39**. Our assumption requires further support from computational studies. Quantitative estima-

Table 5. Effect of leaving group variation on diastereoselectivity in the cyclization of 7-substituted ethyl 2,5-dimethylheptanoate.



44 45

Entry	Leaving gr. Y	Reaction temp. (°C)	Yield (%)	Product ratio (**44/45**)
1	Cl	–20	60.4	70:30
2	TsO	–78	79.0	81:19
3	Br	–78	66.0	79:21
4	TfO	–78	75.0	73:27
5	I	–78	73.0	69:31

tion of the difference in strain energy between diastereomeric foldings in the transition state is desirable, and future studies should addresss this problem by a combination of MO and force field calculations (30, 31). The effect of bulkiness of the substituent on selectivity was examined in the 5-substituted substrate, and selectivity increased in the order Ph < Me ≈ Et < i-Pr < *t*-Bu, as predicted. The effects of the solvent, the base counter cation, and the leaving group are related to enolate reactivity. A greater reactivity is associated with a lower selectivity, i.e., in accord with the normal reactivity–selectivity relationship. These effects should be taken into account when working with diastereoselective ring contruction.

Experimental

IR spectra were obtained on a JASCO A-100 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Hitachi R-90-H, a JEOL FX-100, or a JEOL JMN-GX-400 spectrometer. Proton chemical shifts are reported in ppm on the δ scale relative to TMS as an internal reference (0.00), and carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.03). Carbon signal multiplicities were determined by INEPT experiments. The superscript asterisks on chemical shift values denote the observation of signals for the diastereomer at separate positions. MS spectra (EI) were determined on a JEOL JMS D-300 or a JMX AX-500 high-resolution mass spectrometer. GC analyses were performed on a Shimazu GC-9A apparatus using an OV-1 or Shimazu CBP-20-M-25-20 capillary column. TLC was performed on a precoated thin-layer plate (Merck Art 5744 silica gel $60F_{254}$; 0.25 or 0.5 mm). Silica gel (Fuji–Davison BW-820, BW-300, or BW-200) was used for column chromatography. Et_2O, THF, and DME were distilled from sodium benzophenone ketyl under N_2. HMPA, DMSO, Et_3N, and diglyme were distilled from CaH_2. Benzene, CH_2Cl_2, and CCl_4 were distilled from P_2O_5. MeOH and EtOH were dried by distillation from the corresponding magnesium alkoxide. All reactions were conducted in dry glassware under argon or N_2. The organic extracts were dried over $MgSO_4$ prior to solvent removal on a rotary evaporator.

*3-Benzyloxy-1-propanol (**6**) (32)*

A solution of benzaldehyde (20.4 mL, 200 mmol), 1,3-propanediol (17.4 mL, 240 mmol), and $TsOH{\cdot}H_2O$ (1.9 g) in benzene (300 mL) was refluxed overnight. The reaction mixture was cooled to room temperature, washed successively with 1 N NaOH and water, and dried over anhydrous K_2CO_3. After removal of the solvent the product was distilled to give *3-phenyl-1,3-dioxacyclohexane* (31.4 g, 96%) as a colorless oil; ^1H NMR (90 MHz) δ: 1.20–1.80 (m, 2H, $CH_2CH_2CH_2$), 3.81–4.35 (m, 4H, 2 × OCH_2CH_2), 5.48 (s, 1H, CHPh), 7.20–7.50 (m, 5H, Ph). A solution of this product (15.4 mL, 93.9 mmol) in Et_2O (70 mL) was added to the solution prepared by stirring a mixture of $AlCl_3$ (30.7 g, 230 mmol) in Et_2O (80 mL) and $LiAlH_4$ (2.20 g, 57.5 mmol) in Et_2O (40 mL) at 0°C for 30 min and the resulting mixture was refluxed for 4 h. Water was added carefully to the cooled mixture to destroy the excess hydride and then it was acidified by the addition of dilute H_2SO_4. The mixture was extracted with Et_2O and the combined organic layers were washed with aqueous Na_2CO_3 solution and brine. The product, after removal of the solvent, distilled to afford the title compound **6** (11.2 g, 71%) as a colorless oil; 1H NMR (90 MHz) δ: 1.84 (2H, quintet, J = 5.9 Hz, $CH_2CH_2CH_2$), 1.90 (1H, s, OH), 3.63 (2H, t, J = 5.9 Hz, CH_2CH_2OH), 3.74 (2H, t, J = 5.9 Hz, CH_2CH_2OBn), 4.49 (2H, s, OCH_2Ph), 7.30 (5H, s, Ph).

*1-Benzyloxy-3-bromopropane (**7**)*

To a mixture of 3-benzyloxy-1-propanol (**6**) (11.2 g, 66.7 mmol) and Et_3N (14.0 mL, 100 mmol) cooled to 0°C was added $MeSO_2Cl$ (6.2 mL, 80 mmol). The mixture was stirred for 15 min and the reaction was quenched by the addition of NH_4Cl. The product was extracted with Et_2O and the combined organic phases were washed successively with 1 N HCl, aqueous Na_2CO_3, and brine. The solvent was evaporated to afford the crude mesylate; ^1H NMR (90 MHz) δ: 2.02 (2H, quintet, J = 5.9 Hz, $CH_2CH_2CH_2$), 2.92 (3H, s, O*Ms*), 3.58 (2H, t, J = 5.9 Hz, CH_2OBn), 4.34 (2H, t, J = 5.9 Hz, CH_2OMs), 4.50 (2H, s, OCH_2Ph), 7.31 (5H, s, Ph). A solution of the mesylate thus obtained (16.3 g, 66.7 mmol) in acetone (150 mL) was refluxed overnight with LiBr (14.5 g, 167 mmol) with stirring. Et_2O and water were added and the organic phase was washed with water. The crude product obtained by evaporation of the solvent was purified by silica gel chromatography to furnish the title bromide **7** (12.7 g, 83%) as an oil: ^1H NMR (90 MHz) δ: 2.13 (2H, quintet, J = 6.2 Hz, $CH_2CH_2CH_2$), 3.53 (2H, t, J = 6.2 Hz, CH_2CH_2OBn), 3.66 (2H, t, J = 6.2 Hz, CH_2CH_2Br), 4.51 (2H, s), 7.32 (5H, s, Ph); ^{13}C NMR (25 MHz) δ: 128.5, 127.7, 73.2, 67.7, 32.9, 30.7.

*Ethyl 7-benzyloxy-3-oxoheptanoate (**8**)*

To a stirred suspension of NaH (1.9 g, 39.4 mmol) in THF (50 mL) cooled to 0°C was added a solution of ethyl acetoacetate (4.28 mL, 32.8 mmol) in THF (30 mL). After the mixture had been stirred for 15 min, *n*-butyllithium solution (1.6 M in hexane, 22.0 mL, 35.2 mmol) was added and the mixture was stirred for 15 min at 0°C. To the dianion solution thus prepared was added 3-bromo-1-benzyloxypropane (**7**) (7.51 g, 32.8

mmol) in THF (30 mL) and the reaction mixture was stirred at room temperature for 3 h, then quenched by the addition of 1 N HCl. The product was extracted with Et_2O and the combined organic layers were washed with aqueous $NaHCO_3$ and brine. The residue left after evaporation of the solvent was purified by chromatography on a silica gel column to give the title ester **8** (6.47 g, 71%) as a colorless oil: IR (neat): 1740, 1710 cm^{-1}; ^1H NMR (400 MHz) δ: 1.27 (3H, t, J = 7.3 Hz, $MeCH_2O$), 1.60–1.74 (4H, m, CH_2CH_2), 2.56 (2H, t, J = 6.7 Hz, CH_2CH_2CO), 3.41 (2H, s, $COCH_2CO2$), 3.47 (2H, t, J = 6.7 Hz, CH_2OBn), 4.18 (2H, q, J = 7.3 Hz, OCH_2Me), 4.48 (2H, s, OCH_2Ph), 7.33 (5H, m, Ph); ^{13}C NMR (25 MHz) δ: 202.6 (s), 167.2 (s), 138.5 (s), 128.3 (d), 127.6 (d), 72.9 (t), 69.9 (t), 61.3 (t), 49.3 (t), 42.6 (t), 29.0 (t), 20.3 (t), 14.1 (q).

*Ethyl 7-hydroxy-3-methylheptanoate (**9**)*

To a suspension of NaH (1.46 g, 30.5 mmol) in Et_2O was added a solution of ethyl 7-benzyloxy-3-oxoheptanoate (**8**) (7.7 g, 27.7 mmol) in Et_2O (30 mL) at 0°C. After stirring for 15 min, diethyl chlorophosphate (4.42 mL, 30.5 mmol) in Et_2O (30 mL) was introduced dropwise and stirring was continued at room temperature for 2 h. The reaction mixture was quenched by the addition of aqueous NH_4Cl and washed with aqueous $NaHCO_3$. The solvent was evaporated to leave the enol phosphate. A solution of zero valent palladium reagent was prepared in situ from $PdCl_2(PPh)_3$ (0.38 g, 0.55 mmol) in THF (11 mL) and a solution of DIBAL in toluene (2.25 M, 0.49 mL, 1.1 mmol) at 0°C for 10 min and to this was added successively the enol phosphate (11.4 g, 27.5 mmol), obtained above and dissolved in CH_2Cl_2 (55 mL), and a Me_3Al solution (2 M, 42 mL, 82 mmol) in THF (11 mL). The mixture was stirred at room temperature for 5 days. The reaction mixture was diluted with Et_2O and poured into 1 N HCl. The organic layer was separated and washed with saturated $NaHCO_3$ and brine. The chromatographic purification (silica gel) of the residue left after removal of the solvent afforded *ethyl 7-benzyloxy-3-methyl-2-heptenoate* (6.54 g, 86%) as an oil; ^1H NMR (400 MHz) δ: 1.27 (3H, t, J = 7.3 Hz, $MeCH_2O$), 1.50–1.70 (4H, m), 2.14 (3H, s, =CMe), 2.14 (2H, t, J = 6.1 Hz, CH_2CH_2C=), 3.47 (2H, t, J = 6.1 Hz, CH_2CH_2OBn), 4.14 (2H, q, J = 7.3 Hz, OCH_2Me), 4.49 (2H, s, OCH_2Ph), 5.65 (1H, s, CH=C), 7.33 (5H, m, Ph); ^{13}C NMR (100 MHz) δ: 166.8, 159.6, 138.6, 128.4, 127.6, 127.5, 115.8, 72.9, 70.0, 59.4, 40.6, 29.3, 24.1, 18.6, 14.3. Exact Mass calcd. for $C_{17}H_{24}O_3$: 276.1725; found: 276.1716. A portion of the product (2.4 g, 8.8 mmol) was dissolved in EtOH (50 mL) and hydrogenated in the presence of 10% palladium on charcoal (0.2 g) overnight at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to leave a residue that was purified by chromatography on a silica gel column. The product **9** (1.65 g, 100%) was obtained as a colorless oil; ^1H NMR (400 MHz) δ: 0.93 (3H, d, J = 6.2 Hz, $MeCH$), 1.24 (3H, t, J = 7.0 Hz, $MeCH_2O$), 1.00–2.40 (10H, m), 3.64 (2H, t, J = 5.9 Hz, CH_2CH_2OH), 4.13 (2H, q, J = 7.0 Hz, $MeCH_2O$); ^{13}C NMR (25 MHz) δ: 173.3, 62.9, 60.1, 41.8, 36.4, 32.8, 30.3, 23.1, 19.7, 14.2.

*Ethyl 7-hydroxy-2,3-dimethylheptanoate (**10**)*

A mixture of ethyl 7-hydroxy-3-methylheptanoate (**9**) (1.65 g, 8.8 mmol) and diisopropylethylamine (1.99 mL, 11.4 mmol) in CH_2Cl_2 (35 mL) was stirred for a while at 0°C and then chloromethyl methyl ether (0.87 mL, 11.4 mmol) was added. The resulting mixture was allowed to warm slowly to room temperature, where it was stirred for 5 h, then quenched by the addition of 1 N HCl. The product was extracted with Et_2O, and the extract solution was washed with aqueous $NaHCO_3$ and brine. The residue obtained after evaporation of the solvent was purified by chromatography on a silica gel column to afford *ethyl 7-methoxymethoxy-3-methylheptanoate* (1.92 g, 94%) as an oil: ^1H NMR (400 MHz) δ: 0.94 (3H, d, J = 6.1 Hz, $MeCH$), 1.26 (3H, t, J = 7.3 Hz, $MeCH_2O$), 1.18–2.28 (9H, m), 3.36 (3H, s, $MeOCH_2O$), 3.52 (2H, t, J = 6.1 Hz, CH_2CH_2OMOM), 4.13 (2H, q, J = 7.3 Hz, $MeCH_2O$), 4.62 (2H, s, $MeOCH_2O$). The LDA solution, prepared from diisopropylamine (1.4 mL, 10 mmol) in THF (20 mL) and *n*-butyllithium solution in hexane (1.5 M, 6.8 mL, 10.2 mmol), was cooled to −78°C and to this was added, with stirring, a solution of the MOM ether above dissolved in THF (20 mL) and HMPA (7 mL). After stirring for 30 min, iodomethane (0.62 mL, 10 mmol) was introduced. The cooling bath was removed and the reaction mixture was allowed to warm slowly to room temperature. After 3 h it was quenched by the addition of 1 N HCl and the product was extracted with Et_2O. The organic layers were washed with aqueous $NaHCO_3$ and brine. The residue left after evaporation of the solvent was purified by silica gel chromatography to furnish *ethyl 7-methoxymethoxy-2,3-di-methylheptanoate* (1.69 g, 83%) as an oil: ^1H NMR (400 MHz) δ: 0.86, 0.90* (3H, d, J = 6.6 Hz, $MeCH$), 1.06, 1.10* (3H, d, J = 6.8 Hz, $MeCH_2$), 1.25 (3H, t, J = 7.1 Hz, $MeCH_2O$), 1.10–2.00 (8H, m), 3.36 (3H, s, $MeOCH_2O$), 3.52 (2H, t, J = 6.4 Hz, CH_2CH_2OMOM), 4.13 (2H, q, J = 7.1 Hz, $MeCH_2O$), 4.62 (2H, s, $MeOCH_2O$); ^{13}C NMR (25 Hz) δ: 176.5, 96.5, 67.8, 60.0, 55.1, 44.7,* 44.3, 35.4, 34.6, 33.2,* 29.9, 23.9, 23.7,* 17.2,* 15.7, 14.3, 14.0,* 12.4. Demethoxymethylation of the crude product above (2.35 g) was performed by its treatment with 6 N HCl (4 mL) in THF (47 mL) at room temperature overnight. After dilution with water the reaction mixture was extracted with Et_2O and the combined organic layers were washed with aqueous $NaHCO_3$ and brine. Purification of the product by silica gel chromatography afforded a diastereomeric mixture of the title compound (**10**) (1.76 g, 66% from 9) as an oil: IR (neat): 3375, 1720 cm^{-1}; ^1H NMR (400 MHz) δ: 0.86, 0.91* (3H, d, J = 6.7 Hz, $MeCH$), 1.06, 1.10* (3H, d, J = 6.7 Hz, $MeCH_2$), 1.25 (3H, t, J = 7.3 Hz, $MeCH_2O$), 1.14–1.85 (8H, m), 2.35 (1H, quintet, $CHCHMe$), 3.64 (2H, t, J = 6.1 Hz, CH_2CH_2OH), 4.13 (2H, q, J = 6.7 Hz, $MeCH_2O$); ^{13}C NMR (100 MHz) δ: 176.5(s), 62.9(t), 60.1(t), 60.0(t),* 44.7(d),* 44.3(d), 36.0(d),* 35.4(d), 34.5(t), 33.1(t),* 32.9(t), 23.3(t), 23.2(t),* 17.1(t),* 15.7(q), 14.3(q), 13.9(q), 12.4(q). Exact Mass calcd. for $C_{11}H_{22}O_3$: 202.1569; found: 202.1662.

*Ethyl 7-bromo-2,3-dimethylheptanoate (**11**)*

A mixture of the alcohol **10** (0.57 g, 2.8 mmol) and Et_3N (0.59 mL, 4.2 mmol) in CH_2Cl_2 (10 mL) was stirred at 0°C for 5 min and then $MeSO_2Cl$ (0.26 mL, 3.4 mmol) was added. After the reaction mixture had been stirred for 15 min, it was quenched by the addition of aqueous NH_4Cl. The product was extracted with Et_2O and the extract solution was washed successively with 1 N HCl, aqueous Na_2CO_3, and brine. Evaporation of the solvent gave crude *ethyl 7-mesyloxy-2,3-dimethylheptanoate* as an oil: ^1H NMR (90 MHz) δ: 0.87, 0.91* (3H, d, J = 6.8 Hz, $MeCH$), 1.07, 1.10* (3H, d, J = 7.1 Hz, $MeCH_2$), 1.26 (3H, t, J

= 7.1 Hz, *Me*CH_2O), 1.00–2.00 (7H, m), 2.35 (1H, quintet, J = 6.8 Hz, CHC*H*Me), 3.01 (3H, s, O*Ms*), 4.13 (2H, q, J = 7.3 Hz, MeC*H_2*O), 4.22 (2H, t, J = 6.1 Hz, CH_2CH_2OMs). A solution of the mesylate above in acetone (20 mL) was refluxed with LiBr (0.78 g, 8.9 mmol) overnight. After addition of water the product was extracted with Et_2O and the organic layer was washed with water. The evaporation of the solvent and subsequent purification of the residue by silica gel chromatography afforded the title compound (**11**) (0.50 g, 67%); IR (neat) 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.87, 0.89* (3H, d, J = 7.3 Hz, *Me*CH), 1.07, 1.11* (3H, d, J = 7.3 Hz, *Me*CH), 1.26 (3H, t, J = 6.7 Hz, *Me*CH_2O), 1.15–1.58 (4H, m), 1.76–1.87 (3H, m), 2.35 (1H, quintet, J = 6.7 Hz, CHC*H*Me), 3.41 (2H, t, J = 6.7 Hz, CH_2CH_2Br), 4.14 (2H, q, J = 6.7 Hz, CH_2CH_2O); ^{13}C NMR (100 MHz) δ: 176.4(s), 60.1(t), 44.6(d),* 44.3(d), 35.8(d),* 35.2(d), 33.8(t), 33.7(t), 32.9(t), 25.8(t), 25.6(t),* 17.1(q),* 15.7(q), 14.3(q), 13.8(q),*12.5(q). Exact Mass calcd. for $C_{11}H_{21}O_2Br$: 265.0725; found: 265.0820.

*2-Methyl-5-pentanolide (**12**)*

To a solution of LDA prepared from diisopropylamine (11.9 mL, 85 mmol), THF (100 mL), and *n*-butyllithium solution in hexane (1.3 M, 65 mL, 85 mmol) was added δ-valerolactone (4.63 g, 50 mmol) at −78°C under stirring. After the mixture had been stirred for 30 min, iodomethane (9.34 mL, 150 mmol) dissolved in a mixture of HMPA (10.4 mL) and THF (15 mL) was added dropwise (33). The reaction mixture was allowed to warm slowly, by removal of the cooling bath, up to −40°C, where it was quenched by the addition of water. After acidification with 3 N HCl, the product was extracted with Et_2O and the organic layers were washed with aqueous $NaHCO_3$ and brine. Distillation gave the methylated product **12** (3.57 g, 63%) as a colorless oil; IR (neat): 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 1.26 (3H, d, J = 6.7 Hz, *Me*CH), 1.56 (1H, m, 3-H_{ax}), 1.92 (2H, m, 3-H_{eq}, 4-H_{eq}), 2.10 (1H, sextet, J = 6.7 Hz, 4-H_{ax}), 2.59 (1H, dq, J = 11.0, 6.7 Hz, 2-H), 4.32 (2H, m, 5-C$H_{ax}H_{eq}$); ^{13}C NMR (100 MHz) δ: 175.2, 68.5, 34.6, 27.1, 22.0, 16.7. Exact Mass calcd. for $C_6H_{10}O_2$: 114.0681; found: 114.0697.

*Ethyl 7-hydroxy-2,4-dimethyl-2-heptenoate (**13**)*

To a solution of triethyl 2-phosphonopropionate (11.9 mL, 85 mmol) in THF (100 mL) was successively added *n*-butyllithium solution in hexane (1.4 M, 25.4 mL, 33.8 mmol) and 2-methyl-5-pentanolide (**12**) (3 g, 26 mmol) at −78°C. After stirring of the mixture for a short time, addition of DIBAL solution in toluene (1.76 M, 19.3 mL, 33.8 mmol) followed. The resulting mixture was allowed to react overnight after removal of the cooling bath. The reaction mixture was quenched by the cautious addition of aqueous Na_2SO_4 solution. The precipitate was removed by filtration and the solvent was evaporated from the filtrate. The residue was chromatographed on a column of silica gel, giving the title compound **13** (2.7 g, 60%); ^{1}H NMR (100 MHz) δ: 1.02 (3H, d, J = 6.7 Hz, *Me*CH)), 1.29 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.20–1.70 (5H, m), 1.84 (3H, d, J = 1.3 Hz, MeC═), 2.04 (1H, s, OH), 3.60 (2H, t, J = 6.2 Hz, CH_2CH_2OH), 4.19 (2H, q, J = 7.3 Hz, MeC*H_2*O), 6.59 (1H, dq, J = 10.1, 1.3 Hz, CHC*H*═CMe).

*Ethyl 7-hydroxy-2,4-dimethylheptanoate (**14**)*

The unsaturated ester **13** (2.15 g, 10.75 mmol) dissolved in EtOH (30 mL) was hydrogenated in the presence of 10% palladium on charcoal (0.11 g). Removal of the catalyst by filtration through a short column of silica gel and evaporation of the solvent from the filtrate afforded the title compound **14** (2.085 g, 96%) as an oil; IR (neat): 3400, 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.90 (3H, d, J = 6.7 Hz, *Me*CH), 1.14 (3H, d, J = 7.3 Hz, *Me*CH), 1.25 (3H, t, J = 6.7 Hz, *Me*CH_2O), 1.10–1.80 (8H, m), 2.52 (1H, m, CH_2CHMeCO2), 3.62 (2H, t, J = 6.7 Hz, CH_2CH_2OH), 4.12 (2H, q, J = 6.7 Hz, *Me*CH_2O); ^{13}C NMR (100 MHz) δ: 177.0, 63.2, 60.1, 41.4, 41.1,* 37.5, 33.1, 32.8,* 32.7, 30.7, 30.4,* 19.5, 18.1, 17.2,* 14.2. Exact Mass calcd. for $C_{11}H_{22}O_3$: 202.1569; found: 202.1671.

*Ethyl 7-bromo-2,4-dimethylheptanoate (**15**)*

The alcohol **14** (0.98 g, 4.86 mmol) in CH_2Cl_2 (20 mL) was mesylated with $MeSO_2Cl$ (0.46 mL, 5.84 mmol) and Et_3N (1.02 mL, 7.29 mmol) as before, giving crude *ethyl 7-mesyloxy-2,4-dimethylheptanoate* (1.36 g, ~100%); ^{1}H NMR (400 MHz) δ: 0.91 (3H, d, J = 5.7 Hz, *Me*CH), 1.14 (3H, d, J = 6.6 Hz, *Me*CH), 1.25 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.00–1.93 (6H, m), 2.50 (1H, m, CH_2CHMeCO$_2$), 3.00 (3H, s, OMs), 4.12 (2H, q, J = 7.3 Hz, *Me*CH_2O), 4.20 (2H, t, J = 6.2 Hz, CH_2CH_2OMs); ^{13}C NMR (25 MHz) δ: 176.8, 70.3, 60.1, 41.1, 40.7,* 37.3, 32.7, 32.5,* 30.4, 30.2,* 26.6,* 26.5, 19.4, 19.2,* 18.1, 17.2, 14.2. The mesylate (0.72 g, 2.58 mmol) was converted as before with LiBr (0.56 g, 6.45 mmol) in acetone (9 mL) to afford the title bromide **15** (0.63 g, 92%) as an oil, IR (neat): 1735 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.91 (3H, d, J = 6.7 Hz, *Me*CH), 1.15 (3H, d, J = 6.7 Hz, *Me*CH), 1.26 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.44 (4H, m), 1.72 (1H, m), 1.80 (2H, m), 2.51 (1H, m, CH_2CHMeCO$_2$), 3.39 (2H, t, J = 6.7 Hz, CH_2CH_2Br), 4.13 (2H, q, J = 7.3 Hz, *Me*CH_2O); ^{13}C NMR (100 MHz) δ: 177.0,* 176.9, 60.2,* 60.1, 41.2, 40.9,* 37.4,* 37.3, 35.5, 35.4,* 34.1, 30.34, 30.30,* 30.2,* 30.1,* 19.5, 19.35,* 18.1, 17.2, 14.3. Exact Mass calcd. for $C_{11}H_{21}O_2Br$: 264.0725; found: 264.0808.

*Ethyl 3-methyl-5-pentanolide (**17**) (34)*

To a stirred suspension of $NaBH_4$ (2.0 g, 52.9 mmol) in THF (10 mL) cooled in an ice bath was added 3-methylglutaric anhydride (**16**) (5.93 g, 16.3 mmol) dissolved in THF (50 mL). The ice bath was removed and the mixture was allowed to react for 1 h. After addition of EtOH and acidification with 3 N HCl, the mixture was heated on a water bath for 1 h. The cooled mixture was extracted with Et_2O and the organic layer was washed with aqueous $NaHCO_3$ and brine. Distillation of the product afforded the title lactone **17** (4.01 g, 76%) as an oil; IR (neat): 1730 cm^{-1}; 1H NMR (400 MHz) δ: 1.07 (3H, d, J = 6.1 Hz, *Me*CH), 1.54 (1H, m, 3-H), 1.93 (1H, m, 4-H_{eq}), 2.10 (2H, m, 2-H_{ax}, 4-H_{ax}), 2.68 (1H, m, 2-H_{eq}), 4.27 (1H, td, J = 11.6, 3.7 Hz, 5-H_{ax}), 4.42 (1H, dt, J = 11.6, 4.3 Hz, 5-H_{eq}); ^{13}C NMR (100 MHz) δ: 171.3(s), 68.5(d), 38.2(d), 30.6(t), 26.5(d), 21.4(q).

*Ethyl 7-hydroxy-2,5-dimethylheptanoate (**18**)*

3-Methyl-δ-valerolactone (**17**) (3.65 g, 38.4 mmol) was converted to *ethyl 7-hydroxy-2,5-dimethyl-2-heptenoate* in the same way as in the case of the 2-methyl analog using DIBAL solution (1 M in toluene, 38.4 mL, 32 mmol), triethyl 2-phosphophonopropionate (9.02 mL, 38.4 mmol) in THF (10 mL), and *n*-butyllithium solution (1.6 M in hexane, 26.4 mL, 42.23

mmol). The product (4.77 g, 87%) was obtained as an oil; ^{1}H NMR (400 MHZ) δ: 0.95 (3H, d, J = 6.2 Hz, *Me*CH), 1.30 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.84 (3H, s, MeC=), 1.00–2.00 (5H, m), 2.16 (1H, m), 3.70 (2H, t, J = 7.0 Hz, CH_2CH_2OH), 4.19 (2H, q, J = 7.3 Hz, MeCH_2O), 6.78 (1H, tq, J = 7.3, 1.3 Hz, CH_2CH=CMe). This material (2.33 g, 11.65 mmol) was then hydrogenated with 10% palladium on charcoal (0.31 g) in EtOH (35 mL) to afford the saturated ester **18** (2.48 g, 100%) as an oil; IR (neat): 3450, 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.90 (3H, d, J = 6.7 Hz, *Me*CH), 1.14, 1.15* (3H in total, d, J = 7.3 Hz, *Me*$CHCO_2$), 1.26 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.00–1.80 (6H, m), 2.38 (1H, m, CH_2CHMeCO_2), 3.60 (2H, m, CH_2CH_2OH), 4.13 (2H, q, J = 7.3 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 176.9, 61.1, 61.0,* 60.1, 39.8, 34.5, 34.4,* 34.1, 29.6, 29.4,* 19.6, 17.3, 17.0, 14.3. Exact Mass calcd. for $C_{11}H_{22}O_3$: 202.1569; found: 202.1630.

*Ethyl 7-bromo-2,5-dimethylheptanoate (**19**)*

The hydroxy ester **18** was transformed to *ethyl 7-mesyloxy-2,5-dimethylheptanoate* in the same way as described above. ^{1}H NMR (90 MHz) δ: 0.93 (3H, d, J = 5.7 Hz, *Me*CH), 1.14 (2H, d, J = 6.6 Hz, *Me*CH), 1.25 (3H, t, J = 6.9 Hz, *Me*CH_2O), 1.00–1.80 (8H, m), 2.30 (1H, m, CH_2CHMeCO2), 2.97 (3H, s, OMs), 4.08 (2H, q, J = 7.3 Hz, MeCH_2O), 4.21 (2H, t, J = 6.2 Hz, CH_2OMS). Then the mesylate (3.17 g, 11.3 mmol) was treated with LiBr (2.46 g, 28.3 mmol) in acetone (60 mL), refluxing overnight to furnish the title bromide **19** (1.71 g, 57%) as an oil, IR (neat): 1735 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.90 (3H, d, J = 6.7 Hz, *Me*CH), 1.15 (3H, d, J = 7.3 Hz, *Me*CH), 1.26 (3H, t, J = 6.7 Hz, MeCH_2O), 1.05–1.35 (2H, m), 1.43 (1H, m), 1.65 (3H, m), 1.87 (1H, m), 2.39 (1H, sextet, J = 6.7 Hz, CH_2CHMeCO_2), 3.41 (2H, m, CH_2CH_2Br), 4.13 (2H, q, J = 6.7 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 176.7(s), 60.2(t), 39.8(t) 39.7(d), 33.9(t), 33.8(t),* 31.9(t), 31.6(d), 31.0(t), 30.9(t),* 18.8(q), 17.3(q), 17.0(q), 14.3(q). Exact Mass calcd. for $C_{11}H_{21}O_2$Br: 264.0725; found: 264.0776.

Ethyl 2,5-dimethylheptanoates with various leaving groups at the 7 position

Ethyl 7-chloro-2,5-dimethylheptanoate

A mixture of the hydroxy ester **18** (200 mg, 1.0 mmol), triphenylphosphine (0.63 g, 2.4 mmol), and *N*-chlorosuccinimide (0.37 g, 2.7 mmol) in THF (3 mL) was stirred overnight at room temperature. The usual work-up and chromatographic purification (silica gel) afforded the title chloride (0.17 g, 77%) as an oil; IR (neat) 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.90 (3H, d, J = 6.7 Hz, *Me*CH), 1.15 (3H, d, J = 7.3 Hz, *Me*CH), 1.18 (1H, m), 1.26 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.30 (1H, m), 1.59 (1H, m), 1.64 (2H, m), 1.78 (1H, m), 2.39 (1H, sextet, J = 6.7 Hz, CH_2CHMeCO_2), 3.55 (2H, m, CH_2CH_2Cl), 4.13 (2H, q, J = 7.3 Hz); ^{13}C NMR (100 MHz) δ: 176.7, 60.2, 43.1, 39.7,* 39.6, 33.99, 33.96,* 31.01, 30.98,* 30.4, 19.0, 17.3, 17.0, 14.3. Exact Mass calcd. for $C_{11}H_{21}O_2$Cl: 220.1230; found: 220.1292.

Ethyl 7-iodo-2,5-dimethylheptanoate

The mesylate derived from the hydroxy ester **18** (198 mg, 0.97 mmol) was treated with NaI (0.2 g) in acetone (10 mL) under reflux for 1 h and overnight at room temperature. The usual work-up and subsequent chromatographic purification (silica gel) yielded the title iodide (245 mg, 81%) as an oil, IR (neat): 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.88 (3H, d, J = 6.7 Hz, *Me*CH), 1.15 (3H, d, J = 6.7 Hz, *Me*CH), 1.26 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.10–1.74 (7H, m), 1.86 (1H, m), 2.39 (1H, sextet, J = 6.7 Hz, CH_2CHMeCO_2), 3.15 (1H, dt, J = 8.1, 7.3 Hz, CH_2CH_2I), 3.23 (1H, dt, J = 8.1, 7.3 Hz, CH_2CH_2I), 4.13 (2H, q, J = 7.3 Hz, 2H, MeCH_2O); ^{13}C NMR (100 MHz) δ: 176.7, 60.2, 40.7, 39.8,* 39.7, 33.6, 31.0, 30.9,* 18.6, 17.3, 17.0, 14.3. Exact Mass calcd. for $C_{11}H_{21}O_2$I : 312.0586: found: 312.0572.

Ethyl 7-tosyloxy-2,5-dimethylheptanoate

To a mixture of the hydroxy ester **18** (300 mg, 1.5 mmol), pyridine (0.12 mL, 1.59 mmol), and Et_3N (0.21 mL, 1.59 mmol) in CH_2Cl_2 (3 mL) cooled at 0°C was added tosyl chloride (0.42 g, 2.2 mmol) and the mixture was stirred overnight at room temperature. The crude product obtained by the usual work-up was purified by chromatography on a silica gel column, giving the title tosylate (0.42 g, 83%) as an oil; IR (neat): 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.81 (3H, d, J = 6.1 Hz, *Me*CH), 1.11, 1.12* (3H, d, J = 6.7 Hz, *Me*CH), 1.25 (3H, t, J = 7.3 Hz, MeCH_2O), 1.00–1.74 (4H, m), 2.32 (1H, m, CH_2CHMeCO_2), 2.45 (3H, s, *Me*Ar), 4.06 (2H, m, CH_2CH_2OTs), 4.12 (2H, q, J = 7.3 Hz, MeCH_2O), 7.35 (3H, d, J = 8.5 Hz, Ar*H*), 7.79 (2H, d, J = 8.5 Hz, Ar*H*); ^{13}C NMR (100 MHz) δ: 176.6, 144.7, 133.4, 129.8, 127.9, 68.9, 60.2, 39.73, 39.65,* 35.6, 34.1, 31.0, 30.9,* 29.3, 21.6, 19.0, 17.2,* 17.0, 14.3.

Ethyl 7-trifluoromethanesulfonyloxy-2,5-dimethylheptanoate

A stirred solution of Na_2CO_3 (0.11 g, 1.0 mmol) and trifluoromethanesulfonic anhydride (0.26 mL, 1.56 mmol) in CH_2Cl_2 (3 mL) was cooled to 0°C and the hydroxy ester **18** (264 mg, 1.3 mmol) in CH_2Cl_2 (2 mL) was added. After the mixture had been stirred overnight at room temperature, it was quenched by addition of aqueous $NaHCO_3$ and worked up as usual. Chromatographic purification of the product on a silica gel column furnished the title triflate (274 mg, 78%) as an oil; IR (neat): 1730 cm^{-1}; ^{1}H NMR (90 MHz) δ: 0.95 (3H, d, J = 5.9 Hz, *Me*CH), 1.15 (3H, d, J = 6.8 Hz, *Me*CH), 1.25 (3H, t, J = 7.3 Hz, *Me*CH_2O), 0.8–2.0 (7H, m), 2.18 (1H, m, CH_2CHMeCO_2), 4.13 (2H, q, J = 7.3 Hz, MeCH_2O), 4.58 (2H, t, J = 6.8 Hz, CH_2CH_2OTf).

*Ethyl 7-bromo-5-ethyl-2-methylheptanoate (**25**)*

Vinylmagnesium bromide solution prepared from Mg (0.67 g, 27.5 mmol), vinyl bromide (2.14 mL, 30.3 mmol), and THF (40 mL) was added to a stirred suspension of CuI (0.18 g, 0.92 mmol) in THF (20 mL) at −78°C. After stirring at this temperature for 20 min a solution of 5-pent-2-enolide (**20**) (35) (1.8 g, 18.3 mmol) in THF (10 mL) was introduced and the mixture was stirred for 1 h further, then quenched by the addition of aqueous NH_4Cl. The extraction of the product with ether gave *3-vinyl-5-pentanolide* (1.24 g, 54%) as an oil; ^{1}H NMR (100 MHz) δ: 1.50–2.90 (5H, m), 4.20–4.60 (2H, m, 5-$H_{ax}H_{eq}$), 5.09 (1H, dd, J = 12, 1 Hz, CH=CH_2), 5.14 (1H, dd, J = 9, 1 Hz, CH=CH_2), 5.78 (1H, ddd, J = 12,9,1 Hz, $CHCH$=CH_2). This product was hydrogenated in the presence of palladium on charcoal to give *3-ethyl-5-pentanolide* (**21**) (36) as an oil; ^{1}H NMR (400 MHz) δ: 0.87 (3H, t, J = 7.0

Hz, *Me*CH_2CH), 1.33 (2H, quintet, J = 7.0 Hz, MeCH_2CH), 1.46 (1H, ddt, J = 9.5, 7.4, 5.1 Hz, 3-H), 1.74–1.96 (2H, m, 4-$H_{ax}H_{eq}$), 2.07 (1H, dd, J = 17.2, 10.0 Hz, 2-H_{ax}), 2.62 (1H, ddd, J = 17.4, 6.0, 1.5 Hz, 2-H_{eq}), 4.19 (1H, ddd, J = 11.3, 10.3, 3.5 Hz, 4-H_{ax}), 4.34 (1H, ddd, J = 10.8, 4.8, 4.0, 4-H_{eq}). The lactone **21** (0.69 g, 5.4 mmol) was converted as before by the Takacs procedure (11) to *ethyl 5-ethyl-7-hydroxy-2-methyl-2-heptenoate*, 0.43 g (40%), which on catalytic hydrogenation (10% palladium on charcoal) gave quantitatively *ethyl 5-ethyl-7-hydroxy-2-methylheptanoate* (**23**) as an oil; IR (neat): 1730 cm^{-1}; ^1H NMR (400 MHz) δ: 0.86 (3H, t, J = 7.3 Hz, *Me*CH_2), 1.15 (3H, d, J = 7.3 Hz, *Me*CH), 1.26 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.20–1.70 (10H, m), 2.39 (1H, sextet, J = 7.3 Hz, CH_2CHMeCO_2), 3.66 (2H, t, J = 6.7 Hz, CH_2CH_2OH), 4.13 (2H, q, J = 7.3 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 176.9, 61.1, 60.1, 39.9, 36.4, 35.7, 30.7, 30.6, 25.9, 17.1, 14.3, 10.7. Exact Mass calcd. for $C_{12}H_{24}O_3$: 216.1725; found: 216.1810. The hydroxy ester **23** (0.27 g, 1.23 mmol) was transformed as before via a mesylate to the title bromide **25** (0.23 g, 68%). IR (neat): 1730 cm^{-1}; ^1H NMR (400 MHz) δ: 0.86 (3H, t, J = 7.3 Hz, MeCH_2), 1.15 (3H, d, J = 6.7 Hz, *Me*CH), 1.26 (3H, t, J = 6.7 Hz, MeCH_2O), 1.32 (2H, quintet, MeCH_2CH), 1.20–1.50 (4H, m), 1.63 (1H, m), 1.82 (2H, q, J = 7.3 Hz, CH_2CH_2CH), 2.39 (1H, sextet, J = 6.7 Hz, CH_2CHMeCO_2), 3.41 (2H, t, J = 7.3 Hz, CH_2CH_2Br), 4.13 (2H, q, J = 6.7 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 176.6, 60.2, 39.8, 37.8, 36.6, 31.9, 30.6, 29.95, 25.3, 17.25, 14.3, 10.5. Exact Mass calcd. for $C_{12}H_{23}O_2Br$: 278.0881; found: 278.0967.

*Ethyl 7-bromo-5-isopropyl-2-methylheptanoate (**26**)*

A solution of isopropylmagnesium bromide prepared from isopropyl bromide (1.6 mL, 17 mmol) and Mg (0.38 g, 15.45 mmol) in THF (20 mL) was added to a stirred suspension of CuI (0.1 g, 0.5 mmol) in THF (10 mL) at −78°C. After stirring for 20 min, a solution of 5-pent-2-enolide (**20**) (1.01 g, 10.3 mmol) in THF (5 mL) was introduced and stirring was continued at −78°C for 1 h. Aqueous NH_4Cl was added, and the product was isolated by extraction with Et_2O and was purified by distillation to give *3-isopropyl-5-pentanolide* (**22**) (315 mg, 22%) as an oil; IR (neat): 1720 cm^{-1}; ^1H NMR (400 MHz) δ: 0.92 (3H, d, J = 6.7 Hz, *Me*CH), 0.93 (3H, d, J = 6.7 Hz, *Me*CH), 1.55 (2H, m, 3-H), 1.75 (1H, m, dq, J = 10.7, 6.1, CHC*H*Me_2), 1.92 (1H, dqd, J = 10.4, 4.3, 1.2 Hz, 4-H_{eq}), 2.22 (1H, dd, J = 17.1, 11.0, 2-H_{ax}), 2.66 (1H, ddd, J = 17.1, 4.3, 1.2 Hz, 2-H_{eq}), 4.23 (1H, td, J = 11.0, 3.7 Hz, 5-H_{ax}), 4.41 (1H, dt, J = 11.0, 4.9 Hz, 5-H_{eq}); ^{13}C NMR (100 Hz) δ: 171.9, 68.6, 37.9, 34.1, 32.3, 26.4, 19.3, 19.2. Application of the Takacs procedure (11) on the lactone **22** (314 mg) afforded *ethyl 7-hydroxy-5-isopropyl-2-heptenoate* as an oil, 368 mg (73%). This material was catalytically hydrogenated to give *ethyl 7-hydroxy-5-isopropylheptanoate* as an oil; ^1H NMR (400 MHz) δ: 0.84 (3H, d, J = 6.8 Hz, *Me*CH), 0.85 (3H, d, J = 6.8 Hz, *Me*CH), 1.15 (3H, d, J = 7.3 Hz, CH*Me*CO_2), 1.25 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.10–1.80 (8H, m), 2.39 (1H, sextet, J = 6.8 Hz, CH_2CHMeCO2), 3.65 (2H, m, CH_2CH_2OH), 4.13 (3H, q, J = 7.3 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 176.9, 61.7, 60.2, 40.3, 40.1,* 39.9, 33.7, 33.6,* 31.8, 31.7,* 29.5, 29.4,* 28.3, 19.3, 19.2,* 18.8, 18.7,* 17.2, 14.3. Exact Mass calcd. for $C_{13}H_{26}O_3$: 230.1882; found: 230.1966. The saturated ester (185 mg) was transformed to the bromide as before via a mesylate (163 mg, 71%) giving **26** as an oil; IR (neat) δ: 1730 cm^{-1}; ^1H NMR (400 MHz) δ: 0.86, 1.16* (3H in total, d, J = 6.7 Hz, *Me*CH), 1.26 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.20–1.40 (4H, m), 1.60–1.80 (3H, m), 1.85 (1H, m), 2.40 (1H, sextet, J = 7.3 Hz, CH_2CHMeCO_2), 3.42 (2H, m, CH_2CH_2Br), 4.13 (1H, q, J = 7.3 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 176.6, 60.2, 42.6, 39.91, 39.87,* 34.2, 34.1,* 32.7, 31.63, 31.60,* 29.1, 29.0,* 27.7, 27.6,* 19.2, 19.1,* 18.9, 17.2, 14.3. Exact Mass calcd. for $C_{13}H_{25}O_2Br$: 292.1083; found: 292.0879.

*Ethyl 7-bromo-2-methyl-5-phenylheptanoate (**30**)*

To a mixture of NaOEt solution, prepared from Na (1.38 g, 60 mmol) and EtOH (20 mL), and Et_2O (100 mL) was added diethyl malonate (9.1 mL, 60 mmol) and the mixture was stirred for 30 min. Ethyl cinnamate (10.1 mL, 60 mmol) was added and the reaction mixture was refluxed for 5 h. The cooled mixture was acidified with aqueous acetic acid and the product was extracted with Et_2O. Organic layers were washed with aqueous $NaHCO_3$ and brine, and the solvent was removed by evaporation. Distillation of the residue afforded *diethyl 2-ethoxycarbonyl-3-phenylglutarate* (37) (16.14 g, 73%) as an oil; ^1H NMR (90 mHz) δ: 0.99 (3H, t, J = 7.0 Hz, *Me*CH_2), 1.07 (3H, t, J = 7.0 Hz, *Me*CH_2), 1.18 (3H, t, J = 7.0 Hz, *Me*CH_2), 2.77 (4H, m), 3.93 (2H, q, J = 2.0 Hz, MeCH_2O), 3.97 (2H, q, J = 7.0 Hz, MeCH_2O), 4.21 (2H, q, J = 7.0 Hz, MeCH_2O), 7.24 (5H, s, Ph). The triester was treated with aqueous KOH (14.7 g, 262 mmol, dissolved in 100 mL of H_2O) under refluxing for 1 day. The hydrolysate solution was evaporated in vacuo to dryness and the residue was mixed with diluted H_2SO_4 (26 g with 100 mL of H_2O), and the mixture was refluxed overnight. After concentration in vacuo, the product was extracted with Et_2O to give crude 3-phenylglutaric acid (9.13 g, 100%); ^1H NMR (90 MHz) δ: 2.72 (4H, d, J = 6.7 Hz, 2 × CH_2CH_2CO2), 3.66 (1H, quintet, J = 6.7 Hz, CH_2CHPhCH_2), 7.25 (5H, s), 10.88 (2H, br s, CO2H). This material was heated with Ac_2O under refluxing for 2 h. The reaction mixture was evaporated to dryness in vacuo and the residue was recrystallized from hexane to yield *3-phenylglutaric anhydride* as crystals, 7.73 g (98%). This anhydride (7.73 g, 43.9 mmol) dissolved in THF (50 mL) was added to a solution of $NaBH_4$ (1.7 g, 43.9 mmol) in THF (10 mL) cooled to 0°C. The ice bath was removed and the mixture was allowed to react for 1 h. The reaction mixture was acidified with 3 M HCl, extracted with Et_2O, and the organic layers were washed with aqueous $NaHCO_3$ and brine. Chromatographic purification (silica gel) of the residue left after evaporation of the solvent furnished *3-phenyl-5-pentanolide* (**28**) (38) (1.45 g, 19%) as an oil; IR (neat): 1730 cm^{-1}; ^1H NMR (400 MHz) δ: 2.03 (1H, dtd, J = 14.0, 10.4, 4.9, 4-H_{ax}), 2.18 (1H, dqd, J = 14.0, 3.7, 1.2, 4-H_{eq}), 2.63 (1H, dd, J = 17.7, 10.4, 2-H_{ax}), 2.90 (1H, ddd, J = 17.7, 5.2, 1.2, 2-H_{eq}), 3.24 (1H, tt, J = 10.4 Hz, 3-H), 4.29 (1H, td, J = 11.6, 3.7 Hz, 5-H_{ax}), 4.50 (1H, dt, J = 11.6, 4.9 Hz, 5-H_{eq}), 7.27 (5H, m, Ph); ^{13}C NMR (100 MHz) δ: 170.6, 142.8, 129.0, 127.2, 126.4, 68.6, 37.5, 37.4, 30.3. The lactone **28** was converted as before to *ethyl 7-hydroxy-2-methyl-5-phenyl-2-heptenoate* in 69% yield, this was hydrogenated, giving *ethyl 7-hydroxy-2-methyl-5-phenylheptanoate* (**29**); IR (neat): 3420, 1730 cm^{-1}; ^1H NMR (400 MHz) δ: 1.07, 1.08* (3H, d, J = 7.3 Hz, *Me*CH), 1.22 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.35 (2H, m), 1.48 (1H, m), 1.60 (2H, m), 1.81 (1H, m), 1.92 (1H, m), 2.36 (1H, m), 2.69 (1H, m), 3.45 (1H, m, CH_2CH_2OH), 3.52 (1H, m,

CH_2CH_2OH), 4.09 (2H, q, J = 7.3 Hz, $MeCH_2O$), 7.29 (5H, m, Ph); ^{13}C NMR (100 MHz) δ: 176.7, 144.7, 128.5, 127.6, 126.3, 61.1, 60.1, 42.6, 42.3,* 39.6, 39.5,* 34.4, 34.1,* 31.8, 31.6,* 17.2, 17.0, 14.3. The hydroxy ester **29** (0.34 g) was then transformed via a mesylate to the title bromide **30** in 71% yield. IR (neat): 1730 cm^{-1}; ^1H NMR (400 MHz) δ: 0.88, 1.08* (3H in total, d, J = 7.0 and 6.7 Hz respectively, *Me*CH), 1.23 (3H, t, J = 6.7 Hz, $MeCH_2O$), 1.60 (2H, m), 2.10 (1H, m), 2.35 (1H, m), 2.75 (1H, m), 3.08 (1H, td, J = 6.7, 1.2 Hz, CH_2CH_2Br), 3.26 (1H, td, J = 6.7, 2.4 Hz, CH_2CH_2Br), 4.10 (2H, q, J = 7.3 Hz, $MeCH_2O$), 7.20 (5H, m, Ph); ^{13}C NMR (100 MHz) δ: 176.5, 176.4,* 143.4, 143.3,* 128.6, 127.7, 126.6, 60.1,44.3, 44.1,* 39.7, 39.5,* 34.0, 33.7,* 31.9, 31.7,* 31.6, 31.5,* 22.7, 17.2, 17.1.* Exact Mass calcd. for $C_{16}H_{23}O_2Br$: 326.0881; found: 326.0891.

Ethyl 7-bromo-2-methyl-5-tert-butylheptanoate (35)

A solution of 4-*tert*-butylcyclohexanone (**31**) (15.43 g, 100 mmol), *m*-chloroperbenzoic acid (21.6 g, 125 mmol), and $TsOH{\cdot}H_2O$ (3.5 g) in CH_2Cl_2 (300 mL) was stirred at ambient temperature for 5 h. The precipitate was filtered off and the filtrate was washed successively with aqueous Na_2SO_3, aqueous K_2CO_3, and brine. The residue left after evaporation of the solvent was purified by silica gel chromatography, affording crude *4-tert-butyl-6-hexanolide*, which was used for the next reaction. To the material dissolved in a mixture of THF (120 mL) and Et_2O (80 mL) was added a 1 M methyllithium solution in THF (120 mL, 120 mmol) at −90°C and the mixture was stirred at this temperature for 3 h. After quenching by the addition of aqueous NH_4Cl, the reaction mixture was extracted with Et_2O and the product was purified by chromatography on a silica gel column, giving *6-oxo-3*-tert-*butyl-1-heptanol* (13.82 g, 74% from **31**) as an oil; IR (neat): 3420, 1710 cm^{-1}; ^1H NMR (400 MHz) δ: 0.88 (9H, s, Me3C), 1.28 (2H, m), 1.78 (3H, m), 1.89 (1H, br s, OH), 2.15 (3H, s, MeCO), 2.50 (2H, m, CH_2CH_2CO), 3.65 (2H, t, J = 6.7 Hz, CH_2CH_2OH). A solution of the alcohol (13.8 g, 74.3 mmol), imidazole (12.6 g, 185 mmol), and *tert*-butyldimethylsilyl chloride (13.4 g, 90 mmol) in DMF (30 mL) was stirred at ambient temperature for 1 day, and then the reaction mixture was quenched by the addition of aqueous NH_4Cl. Purification of the product by silica gel chromatography afforded 5-tert-*butyl-7*-tert-*butyldimethylsilyloxy-2-heptanone* (**32**) (12.94 g, 58%) as an oil; IR (neat): 1720 cm^{-1}; ^1H NMR (400 MHz) δ: 0.05 (6H, s, SiMe2), 0.86 (9H, s, $SiBu^t$), 0.90 (9H, s, Me_3C), 1.26 (2H, m), 1.75 (2H, m), 2.12 (3H, s, MeCO), 2.38 (1H, ddd, J = 15.9, 10.3, 6.1 Hz, CH_2CH_2CO), 2.56 (1H, ddd, J = 15.9, 11.0, 5.5 Hz, CH_2CH_2CO), 3.57 (2H, t, J = 6.7 Hz, CH_2CH_2OSi); ^{13}C NMR (100 MHz) δ: 233.9, 63.4, 44.4, 43.7, 34.4, 33.9, 29.9, 27.6, 26.0, 25.4, 18.4. Exact Mass calcd. for $C_{17}H_{36}O_2Si$: 300.2485; found: 300.2556. A solution of the silyl ether **32** (1.4 g, 4.7 mmol) in anhydrous Et_2O was added at −25°C to a solution of methoxymethylenetriphenylphosphorane prepared from methoxymethyltriphenylphosphonium chloride (2.4 g, 7 mmol), 1.6 M *n*-butyllithium solution in hexane (4.4 mL, 7 mmol), and Et_2O (20 mL). The mixture was stirred at −20°C for 1 h and at room temperature for 3 h. After removal of the precipitate by filtration the filtrate was washed with cold water and brine. The crude enol ether obtained by evaporation of the solvent was added to a mixture of 70% aqueous perchloric acid and Et_2O (60 mL), and the mixture was allowed to react at room temperature for 2 h. The reaction mixture was washed successively with water, aqueous $NaHCO_3$, and brine. Evaporation of the solvent gave crude *ethyl 7-hydroxy-2-methyl-5-tert-butylheptanal* (**33**); ^1H NMR (400 MHz) δ: 0.86 (9H, s, Me_3C), 1.10 (3H, d, J = 7.0 Hz, *Me*CH), 0.80–2.00 (9H, m), 3.63 (3H, t, J = 7.3 Hz, CH_2CH_2OH), 9.61 (1H, d, J = 1.2 Hz, CH_2CHO). To a stirred solution of the aldehyde **33** (4.2 g, 21 mmol) in a mixture of *tert*-BuOH (60 mL) and 5% aqueous NaH_2PO_4 was added dropwise 1 M aqueous $KMnO_4$ solution (50 mL, 50 mmol) (39) and stirring was continued at room temperature for 5 h. The reaction mixture was diluted with water and the product was isolated by extraction with Et_2O, giving the corresponding carboxylic acid, which was esterified by refluxing with 3 M HCl, EtOH (15 mL), and toluene (7 mL) for 5 h. Usual work-up afforded *ethyl 7-hydroxy-2-methyl-5*-tert-*butylheptanoate* (**34**). This hydroxy ester was converted via a mesylate to the title bromide **35**; IR (neat): 1730 cm^{-1}; ^1H NMR (400 MHz) δ: 0.87 (9H, s, Me_3C), 1.02 (2H, m), 1.16 (3H, d, J = 6.7 Hz, *Me*CH), 1.26 (3H, t, J = 6.7 Hz, $MeCH_2O$), 1.30–1.80 (4H, m), 2.04 (1H, m), 2.39 (1H, m, $CH_2CHMeCO_2$), 3.38 (1H, dt, J = 8.6, 7.3 Hz, $CH_2CH_aH_bBr$), 3.46 (2H, tdd, J = 9.5, 5.5, 2.4 Hz, $CH_2CH_aH_bBr$), 4.14 (2H, q, J = 6.7 Hz, $MeCH_2O$). Exact Mass calcd. for $C_{14}H_{27}O_2Br$: 306.1194; found: 306.1296.

4-Methyl-5-pentanolide (37)

A mixture of methacrolein (14.8 mL, 143 mmol), dimethyl malonate (14.1 mL, 120 mmol), and Et_3N (16.7 mL, 120 mmol) in MeOH (150 mL) was stirred at 0°C for 17 h (40). The product obtained by Et_2O extraction was distilled, giving *dimethyl 3-formyl-1,1-butanedicarboxylate* (10.1 g, 41%); ^1H NMR (90 MHz) δ: 1.15 (3H, d, J = 7 Hz, $MeCH_2O$), 1.66–2.57 (3H, m), 3.47 (1H, m, $CH_2CH(CO_2Me)_2$), 3.71 (6H, s, 2 × CO_2Me), 9.57 (1H, br s, CH_2CHO). The aldehyde (4.2 g, 20.8 mmol) dissolved in MeOH (10 mL) was treated with a solution of $NaBH_4$ (0.79 g, 20.8 mmol) in MeOH (10 mL) at room temperature for 1.5 h. After addition of 3 M HCl, the mixture was concentrated and then extracted with Et_2O. Evaporation of the solvent afforded crude *dimethyl 4-hydroxy-3-methyl-1,1-butanedicarboxylate* (**36**) (4.0 g, 94%); ^1H NMR (90 MHz) δ: 0.93 (3H, d, J = 7 Hz, *Me*CH), 1.30–2.25 (4H, m), 3.43 (2H, d, J = 6 Hz, $CHCH_2OH$), 3.69 (6H, s, 2 × CO_2Me). The alcohol **36** (3.82 g, 18.7 mmol) was heated under refluxing with NaOH (4.73 g, 84.3 mmol) and water (6 mL) for 3 h. The mixture was diluted with water (6 mL) and concentrated. It was mixed with concentrated H_2SO_4 (5.8 g), diluted with water (7 mL), and the mixture was refluxed for 3 h. Extraction with Et_2O gave the crude title compound **37** (2.03 g, 95%); ^1H NMR (90 MHz) δ: 0.98 (3H, d, J = 6 Hz, *Me*CH), 1.13–2.83 (5H, m), 2.43 (1H, m, 2-H_{eq}), 3.84 (1H, dd, J = 12, 10 Hz, 5-H_{ax}), 4.27 (1H, ddd, J = 12, 5, 2 Hz, 5-H_{eq}).

Ethyl 7-bromo-2,6-dimethylheptanoate (39)

The lactone **37** (1.38 g, 12 mmol) was converted by Takacs' procedure (11) as before to furnish *ethyl 7-hydroxy-2,6-dimethyl-2-heptenoate* (1.62 g, 70%); ^1H NMR (90 MHz) δ: 0.93 (3H, d, J = 6 Hz, *Me*CH), 1.07–1.70 (9H, m), 1.81 (3H, br s, *Me*C=), 3.43 (2H, d, J = 6 Hz, $CHMeCH_2OH$), 4.15 (2H, q, J = 6 Hz, $MeCH_2O$), 6.70 (1H, br t, J = 7 Hz, CH_2CH=). The unsaturated alcohol was catalytically hydrogenated (Pd–C) to

give *7-hydroxy-2,6-dimethylheptanoate* (**38**); ^{1}H NMR (90 MHz) δ: 0.90 (3H, d, J = 6 Hz, *Me*CH), 1.03–2.40 (15H, m), 3.42 (2H, m), 4.17 (2H, q, J = 6 Hz, MeCH_2O). The saturated hydroxy ester **38** was mesylated as before to yield *ethyl 7-mesyloxy-2,6-dimethylheptanoate*; ^{1}H NMR (90 MHz) δ: 0.97 (3H, d, J = 7 Hz, *Me*CH), 1.15–2.60 (14H, m), 2.95 (3H, s, MsO), 4.00 (2H, d, J = 6 Hz, CH_2CH_2OMs), 4.08 (2H, q, J = 7 Hz, MeCH_2O). Treatment of this mesylate with LiBr in acetone afforded the title bromide **39** (51% from mesylate); ^{1}H NMR (90 MHz) δ: 0.97 (3H, d, J = 6 Hz, *Me*CH), 1.23 (3H, t, J = 7 Hz, *Me*CH_2O), 0.78–2.10 (7H, m), 2.40 (1H, sextet, J = 6.0 Hz, CH_2CHMeCO$_2$), 3.30 (2H, d, J = 6 Hz, CHMeCH_2Br), 4.07 (2H, q, J = 7 Hz, MeCH_2O); ^{13}C NMR (25 MHz) δ: 176.5, 60.1, 41.3, 39.4, 35.0, 34.6, 33.8,* 24.4, 18.7, 17.1, 14.3.

*Cyclization of ethyl 7-bromo-2,3-dimethylheptanoate (**11**).*

Typical procedure for cyclization experiments

A mixture of diisopropylamine (0.51 mL, 1.0 mmol) in THF (5 mL) and *n*-butyllithium solution (1.6 M in hexane, 2.0 mL, 3.2 mmol) was stirred at 0°C for 10 min and then the stirring was continued at −78°C for 20 min. To this solution was added a solution of the ester **11** (265 mg, 1.00 mmol) and the mixture was allowed to react at −78°C for 1 h. After quenching by the addition of aqueous NH_4Cl, the reaction mixture was extracted with Et_2O and the combined organic layers were washed with brine. The residue left after evaporation of the solvent was purified by chromatography on a silica gel column, giving the cyclized product (193 mg, 78%), which was a 96:4 mixture of diastereomers (capillary GC). From the reason discussed in the text, the major isomer was identified as *ethyl 1,*t*-2-dimethyl*-r-*1-cyclohexanecarboxylate* (**40**); IR (neat): 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.77 (3H, d, J = 6.7 Hz, *Me*CH), 1.07 (3H, s, *Me*C), 1.25 (3H, t, J = 6.7 Hz, *Me*CH_2O), 1.00–1.60 (6H, m), 2.01 (1H, dqd, J = 10.5, 6.7, 3.1 Hz, 2-H), 4.13 (2H, q, J = 6.7 Hz, *Me*CH_2O); ^{13}C NMR (100 MHz) δ: 178.5(s), 60.1(t), 46.5(d), 36.1(s,t), 29.9(t), 25.4(t), 21.3(t), 17.3(q), 14.3(q), 14.1(q). Exact Mass calcd. for $C_{11}H_{20}O_2$: 184.1463; found: 184.1455.

*Cyclization of ethyl 7-bromo-2,4-dimethylheptanoate (**15**)*

The reaction afforded exclusively *ethyl 1,*c*-3-dimethyl*-r-*1-cyclohexanecarboxylate* (**42**); IR (neat): 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.75–0.85 (2H, m), 0.88 (3H, d, J = 6.7 Hz, *Me*CH), 1.00–1.06 (1H, m), 1.20 (3H, t, J = 6.8 Hz, *Me*CH_2O), 1.28–1.90 (6H, m), 4.11 (2H, q, J = 6.8 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 178.9(s), 60.2(t), 42.5(t), 42.4(s), 34.7(t), 33.4(t), 27.4(d), 22.8(q), 21.4(t), 20.5(q), 14.2(q). Exact Mass calcd. for $C_{11}H_{20}O_2$: 184.1463; found: 184.1468.

*Cyclization of ethyl 7-bromo-2,5-dimethylheptanoate (**19**)*

The diasteromeric ratio of the cyclized product was 79:21 and both diastereomers were separated by flash chromatography on a silica gel column for the purpose of the spectroscopic analysis. A *trans* and a *cis* structure was assigned for the major and the minor diastereomers, respectively. *Ethyl 1,*t*-4-dimethyl*-r-*1-cyclohexanecarboxylate* (**44**): ^{1}H NMR (400 MHz) δ: 0.91 (3H, d, J = 6.7 Hz, *Me*CH), 1.10 (2H, td, J = 13.4, 3.6 Hz, 2,6-H_{ax}), 1.18 (3H, s, MeC), 1.24 (3H, t, J = 6.7 Hz, *Me*CH_2O), 1.37 (1H, m, 4-H), 1.58 (4H, m, 2,6-H_{eq}, 3,5-H_{eq}), 1.69 (2H, qd, J = 13.4, 3.7 Hz, 3,5-H_{ax}), 4.11 (2H, q, J = 6.7 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 178.9(s), 60.1(t), 41.6(s), 33.4(t), 31.6(d), 30.0(t), 21.9(q), 20.8(q), 14.2(q). Exact Mass calcd for $C_{11}H_{20}O_2$: 184.1463; found: 184.1474. *Ethyl 1,*c*-4-dimethyl*-r-*1-cyclohexanecarboxylate* (**45**); ^{1}H NMR (400 MHz) δ: 0.85 (3H, d, J = 6.7 Hz, *Me*CH), 0.96 (2H, qd, J = 13.4, 2.5 Hz, 3,5-H_{ax}), 1.12 (2H, td, 2H, J = 13.4, 3.7 Hz, 2,6-H_{ax}), 1.13 (3H, s, MeC), 1.25 (3H, t, J = 6.7 Hz, MeCH_2O), 1.28 (1H, m, 4-H), 1.56 (2H, m, 3,5-H_{eq}), 2.17 (2H, br. d, J = 13.4 Hz, 2,6-H_{eq}), 4.14 (2H, q, J = 6.7 Hz, *Me*CH_2O); ^{13}C NMR (100 MHz) δ: 177.4, 60.0, 43.1, 36.0, 32.5, 32.1, 28.3, 22.4, 14.3. Exact Mass calcd. for $C_{11}H_{20}O_2$: 184.1463; found: 184.1454.

*Cyclization of ethyl 7-bromo-5-ethyl-2-methylheptanoate (**25**)*

The major and the minor products were separated by the flash chromatography and analyzed by spectroscopy to be *trans* and *cis* compounds, respectively. *Ethyl* t*-4-ethyl-1-methyl*-r-*1-cyclohexanecarboxylate* (**46**). ^{1}H NMR (400 MHz) δ: 0.88 (3H, t, J = 7.3 Hz, 4-*Me*CH_2), 1.17 (3H, s, MeC), 1.24 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.06–1.30 (5H, m, 2,6-H_{ax}, 4-H, 4-MeCH_2), 1.63 (6H, m, 2,6-H_{eq}, 3,5-$H_{ax}H_{eq}$), 4.11 (2H, q, J = 7.3 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 178.9(t), 60.1(t), 41.9(s), 38.4(d), 33.4(t), 29.1(t), 27.6(t), 20.7(q), 14.2(q), 11.5(q). Exact Mass calcd for $C_{12}H_{22}O_2$: 198.1620; found: 198.1643. *Ethyl* c*-4-ethyl-1-methyl*-r-*1-cyclohexanecarboxylate* (**47**): ^{1}H NMR (400 MHz) δ: 0.85 (3H, t, J = 7.3 Hz, 4-*Me*CH_2), 0.94 (2H, qd, J = 13.4, 2.5 Hz, 3,5-H_{ax}), 1.06 (1H, m, 4-H), 1.10 (2H, td, J = 12.8, 3.4 Hz, 2,6-H_{ax}), 1.13 (3H, s, MeC), 1.25 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.64 (2H, br d, J = 13.4 Hz, 3,5-H_{eq}), 2.19 (2H, br d, J = 13.4 Hz, 2,6-H_{eq}), 4.13 (2H, q, 2H, J = 7.3 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 177.4(s), 60.0(t), 43.5(s), 38.8(d), 35.9(t), 30.1(t), 29.7(t), 28.3(q), 14.3(q), 11.5(q). Exact Mass calcd. for $C_{12}H_{22}O_2$: 198.1620; found: 198.1646.

*Cyclization of ethyl 7-bromo-5-isopropyl-2-methylheptanoate (**26**)*

Major product: *ethyl* t*-4-isopropyl-1-methyl*-r-*1-cyclohexanecarboxylate* (**48**); ^{1}H NMR (400 MHz) δ: 0.87 (6H, d, J = 6.7 Hz, Me_2CH), 1.02 (1H, m, 4-H), 1.17 (3H, s, MeC), 1.20 (2H, m, 2,6-H_{ax}), 1.24 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.44 (1H, octet, J = 6.7 Hz, Me_2CHCH), 1.57 (2H, dq, J = 12.2, 4.3 Hz, 3,5-H_{eq}), 1.67 (4H, m, 2,6-H_{eq}, 3,5-H_{ax}), 4.11 (2H, q, J = 7.3 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 179.0(s), 60.1(t), 43.5(d), 36.2(t), 32.7(d), 28.4(q), 27.2(t), 24.7(t), 19.9(q), 14.3(q). Exact Mass calcd. for $C_{13}H_{24}O_2$: 212.1776; found: 212.1797. Minor product: *ethyl* c*-4-isopropyl-1-methyl*-r-*1-cyclohexanecarboxylate* (**49**); ^{1}H NMR (400 MHz) δ: 0.83 (6H, d, J = 6.7 Hz, Me_2CH), 0.98–1.12 (5H, m, 2,6-H_{ax}, 3,5-H_{ax}, 4-H), 1.12 (3H, s, MeC), 1.25 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.37 (1H, m, Me_2CH), 1.64 (2H, br, d, J = 6.7 Hz, 3,5-H_{eq}), 2.21 (2H, br d, J = 12.2 Hz, 2,6-H_{eq}), 4.14 (2H, q, J = 7.3 Hz, MeCH_2O); ^{13}C NMR (100 MHz) δ: 177.4(s), 60.0(t), 43.5(d,s), 36.2(t), 32.7(d), 28.4(q), 27.2(t), 24.7(t), 19.9(q), 14.3(q). Exact Mass calcd. for $C_{13}H_{24}O_2$: 212.1776: found 212.1791.

*Cyclization of ethyl 7-bromo-2-methyl-5-phenylheptanoate (**30**)*

Major product: *ethyl 1-methyl*-t*-4-phenyl*-r-*1-cyclohexanecarboxylate* (**50**); IR (neat): 1730 cm^{-1}; ^{1}H NMR (400 MHz)

δ: 1.27 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.29 (3H, s, MeC), 1.68 (2H, qd, J = 12.2, 3.1 Hz, 3,5-H_{ax}), 1.80 (4H, m, 2,6-H_{ax}, 3,5-H_{eq}), 1.84 (2H, td, J = 12.2, 3.7 Hz, 2,6-H_{eq}), 2.50 (1H, tt, J = 12.2, 3.7 Hz, 4-H), 4.15 (2H, q, J = 7.3 Hz, MeC*H*$_2$O), 7.26 (5H, m, Ph); ^{13}C NMR (100 MHz) δ: 178.8, 147.0, 128.4, 126.8, 126.1, 60.3, 43.7, 41.3, 34.1, 29.0, 20.1, 14.2. Exact Mass calcd. for $C_{16}H_{22}O_2$: 246.1620; found: 246.1616. Minor product: *ethyl 1-methyl*-c-*4-pheny*-r-*1-cyclohexanecarboxylate* (**51**); IR (neat): 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ: 1.20 (3H, s, MeC), 1.28 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.30 (2H, m, 2,6-H_{ax}), 1.53 (2H, qd, J = 13.4, 3.1 Hz, 3,5-H_{ax}), 1.80 (2H, br d, J = 13.4 Hz, 3,5-H_{eq}), 2.33 (2H, br d, J = 12.2 Hz, 2,6-H_{eq}), 2.47 (1H, tt, J = 13.4, 3.7 Hz, 4-H), 4.19 (2H, q, J = 7.3 Hz, *Me*CH_2O), 7.26 (5H, m, Ph); ^{13}C NMR (100 MHz) δ: 177.2, 147.2, 128.3, 126.8, 126.0, 60.2, 43.8, 43.1, 36.3, 31.6, 28.4, 14.3. Exact Mass calcd. for $C_{16}H_{22}O_2$: 246.1620; found: 246.1615.

Cyclization of ethyl 7-bromo-2-methyl-5-tert-*butylheptanoate (35)*

Major product: *ethyl 1-methyl*-t-*4*-tert-*butyl*-r-*1-cyclohexanecarboxylate* (**52**); ^{1}H NMR (400 MHz) δ: 0.86 (s, 9H, Me_3C), 0.98 (1H, tt, J = 12.2, 3.1 Hz, 4-H), 1.17 (3H, s, MeC), 1.18 (2H, m, 2-H_{ax}), 1.24 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.59–1.75 (6H, m, 2,6-H_{eq}, 3,5-$H_{ax}H_{eq}$), 4.11 (2H, q, J = 7.3 Hz, MeC*H*$_2$O); ^{13}C NMR (100 MHz) δ: 179.1, 60.1, 47.8, 41.4, 34.4, 32.4, 27.5, 22.2, 19.7, 14.2. Exact Mass calcd. for $C_{14}H_{26}O_2$: 226.1933; found: 226.1905. Minor product: *ethyl 1-methyl*-c-*4*-tert-*butyl-1-cyclohexanecarboxylate* (**53**); ^{1}H NMR (400 MHz) δ: 0.81 (9H, s, Me_3C), 0.90–1.15 (5H, m, 2,6-H_{ax}, 3,5-H_{ax}, 4-H), 1.12 (3H, s, MeC), 1.25 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.64 (2H, m, 3,5-H_{eq}), 2.23 (2H, dt, J = 11.0, 3.2 Hz, 2,6-H_{eq}), 4.15 (2H, q, J = 7.3 Hz, MeC*H*$_2$O); ^{13}C NMR (100 MHz) δ: 177.4, 60.0, 47.6, 43.3, 36.6, 32.4, 28.4, 27.5, 24.8, 14.3. Exact Mass calcd. for $C_{14}H_{26}O_2$: 226.1933; found: 226.1915.

Cyclization of ethyl 7-bromo-2,6-dimethylheptanoate (39)

The reaction yielded the same diastereomeric 1,3-dimethylcyclohexane derivatives as in the case of the bromide **15** but with the reversed predominance — the dominant product was *ethyl 1,* t-*3-dimethyl*-r-*1-cyclohexanecarboxylate* (**43**); ^{1}H NMR (400 MHz) δ: 0.72 (1H, t, J = 12.5 Hz, 2-H_{ax}), 0.79 (1H, qd, J = 13.5, 3.7 Hz. 4-H_{ax}), 0.87 (3H, d, J = 6.7 Hz, *Me*CH), 0.98 (1H, td, J = 13.5, 4.0 Hz, 6-H_{ax}), 1.13 (3H, s, MeC), 1.24 (3H, t, J = 7.3 Hz, *Me*CH_2O), 1.32 (1H, qt, J = 13.5, 3.7 Hz, 5-H_{ax}), 1.41 (1H, m. 3-H), 1.58 (1H, m, 5-H_{eq}), 1.62 (2H, m, 4-H_{eq}), 2.13 (1H, dq, J = 12.5, 2.4 Hz, 2-H_{eq}), 2.16 (1H, br d, J = 13.5 Hz, 6-H_{eq}), 4.13 (2H, q, J = 7.3 Hz, MeC*H*$_2$O); ^{13}C NMR (100 MHz) δ: 177.5, 60.0, 44.8, 43.9, 35.7, 34.5, 29.9, 28.7, 23.8, 22.8, 14.3.

Acknowledgement

We thank Dr. Yoshinosuke Usuki for his assistance.

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