Diastereofacial Selection in Ring-Closure Reactions and Folding-Strain Stereocontrol

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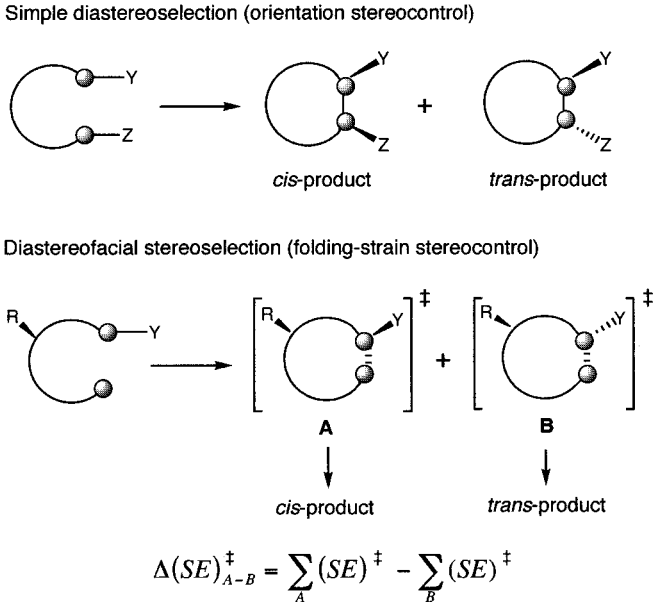
Abstract: The potential of diastereofacially selective ring-closure reactions in organic synthesis is advanced by the concept of folding-strain stereocontrol, that is, the use of the energy balance among diastereomeric foldings of an acyclic chain to determine the selectivity, which defines the difference from intermolecular reactions. For generalization of the concept, the diastereofacial selectivity and the factors affecting the folding strain have been investigated in cyclizations of two types of substrates with substituents at various positions on the acyclic chains—2-(6′-trimethylsilylhex-4′-enyl)cyclohexene-2-ones and ethyl 7-bromo-2-methylhexanoates. Diastereoselectivity ranged from moderate to excellent, being subtly affected by the relative positions of a substituent to the forming bond. The conformational analysis of diastereomeric transition states is the central issue in the design of a diastereofacially selective ring-closure reaction. In addition, the effects on diastereofacial selectivity as regard substituent bulkiness, types of the reaction, and controlling substituents are discussed.

Keywords: conformation analysis · folding-strain stereocontrol · ring closure · stereoselective synthesis · transition states

Diastereoselective cyclization reactions are an effective means for the synthesis of cyclic natural products, since ring formation and construction of the diastereomeric centers are achieved at the same time. In fact cycloaddition reactions represented by the Diels–Alder reaction are often highly stereoselective and have been extensively utilized in stereoselective syntheses.[1] In contrast, simple ring-closure reaction has attracted far less attention for this purpose, probably because of the view that marked diastereoselectivity could not be expected, since the transition state (TS) conformation could be more flexible than the TS in the cycloaddition reactions.[2] This is rather surprising, since effective diastereoselection in reactions involving cyclic intermediates or cyclic TSs are exemplified abundantly in connection with acyclic stereocontrol.[3]

In ring-closure reactions, two types of diastereoselection are distinguished, namely simple diastereoselection and diastereofacial selection,[4] as in intermolecular cases[5, 6] (Scheme 1). The former is concerned with the mutual disposition of two diastereotopic reaction centers, and is regulated stereoelectronically and sterically. The problems associated with this type of stereoselection have been recently studied for aldol-type[5, 6] or allylmetal reactions.[7, 8] The latter type of diastereoselection represents the diastereodifferentiation of the newly forming bond relative to the stereogenic center present in the chain and has to do with a relative asymmetric induction. In the present article, the discussion is focused on this type of diastereocontrol, which is designated as folding-strain stereocontrol.[9–12] Whereas in the literature there are many instances of ring-closure reactions of various



Scheme 1. Two types of diastereoselection in ring-closure reactions.

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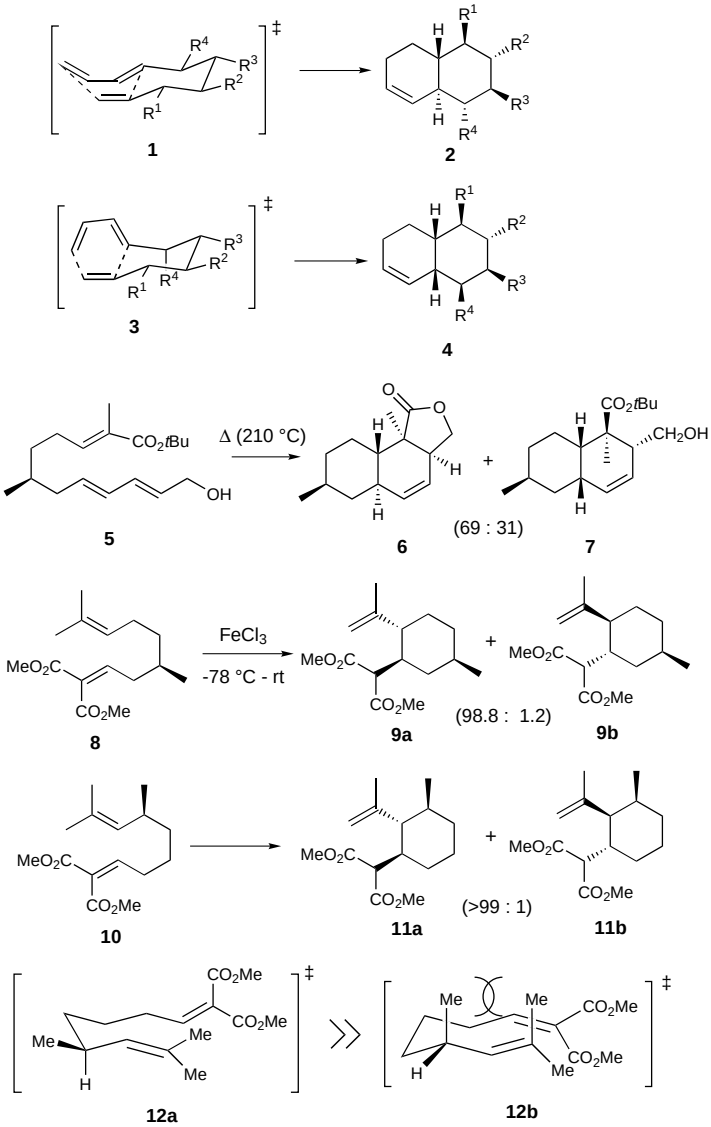
types in which high diastereofacial selectivity is observed, an attempt to conceptualize diastereofacially selective ring-closure reactions as a whole appears to be lacking and its application in the synthesis of complex natural products is still very limited. The purpose of this article is to explain folding-strain stereocontrol as a convenient guiding concept and to exemplify the potential of diastereofacially selective ring-closure reaction as a stereoselective methodology.

Diastereofacially selective ring-closure reactions: Many examples occur in the intramolecular Diels–Alder (IDA) reaction and in radical cyclization. In the IDA reactions, where one or more substituents are present in the chain tethering diene and dienophile groups, the diastereofacial selectivity with respect to these is a concern additional to the *endo/exo* problem.[13, 14] This problem has been summarized by Roush[14] for the reactions of conformationally mobile monosubstituted 1,7,9-decatrienones and 1,6,8-nonatrienones (only the former case is depicted in Scheme 2). In both of the reactions in *trans*-fused (*endo*) and *cis*-fused (*exo*) manner, the formation of **2** and **4** with any of R^1, R^2, or R^3 in equatorial conformation is preferred; this is rationalized by the consideration of chairlike TSs **1** and **3** with the substituents in more stable equatorial conformation. As concerns the R^4 substituent, its equatorial disposition is usually favored for the *trans*-TS **1**, while in the *cis*-TS **3**, an axial conformation could be prefered owing to the $A^{1,3}$ strain[15, 16] present in the equatorial counterpart. Additionally, when the R^1 is a polar and sterically less demanding group like an alkoxy group, the stereoelectronic effect may intervene and its axial disposition can be favored.[13a, 14] The degree of the diastereofacial selectivity in the IDA reactions ranges from fair to excellent. The IDA reaction of triene ester **5** is, for instance, reported to give a mixture of *trans* and *cis* products, **6** and **7**,[17] both of which have secondary methyl groups in equatorial dispositions in accordance with the description above. Diastereofacial selectivity in the intramolecular ene reactions (IE) of 1,6- or 1,7-dienes with methyl groups in the chains was studied by Tietze in some detail,[18] and, under conditions of Lewis acid catalysis, substrates **8** and **10** were reported to give cyclized products **9** and **11**, respectively, the diastereoselectivity being higher for the latter case, where an $A^{1,3}$ strain is additionally operative in the TS (**12a** ≫ **12b**). Notably, the selectivity in the former reaction **8** → **9** is still considerably higher than would be expected from comparison with the comformational free energies of the methyl group in methylcyclohexane ($\Delta G^\circ = -1.74$ kcal mol^{-1}).[18c] The reaction **8** → **9** provided a method for an efficient preparation of the key intermediate for enantioselective synthesis of marine terpenoids, pseudopterosins.[19] With the recent rapid growth of the synthetic utility of radical reactions,[20, 21] the diastereofacial selection in the intramolecular reactions of substituted hexenyl and heptenyl radicals was studied extensively and has been generalized on the basis of the Beckwith–Houk model.[22] Although this TS model is concerned essentially with 5-*exo* cyclization of hexenyl radicals to form cyclopentanes, the diastereofacial selection in the 6-*exo* cyclization of substituted heptenyl radicals can be rationalized by similar consideration as in the Beckwith–Houk model—preference of the chairlike TS (cf. **16a** and **16b**) with an equatorial substituent. A representative example is the radical cyclization of 6-alkyl-8-bromo-2-octenoic acid esters **13**–**15**, which affords a mixture of *trans*- and *cis*-cyclohexane derivatives, **17a** and **17b**, respectively (Scheme 3). The former formed preferentially, and the diastereofacial selectivity was higher for the *Z* substrate. Since the steric bulk of the substituents did not substantially affect the selectivity, its difference as regards double-bond geometry was explained by the disposition of the unsaturated ester groups in TSs—namely the preference for TS **16a** over TS **16b** (in the case of the *Z* substrate, Y = H and Z = CO_2R^2!), the substituents being locked in equatorial positions in both TSs. For application to the stereoselective synthesis of cyclic natural products, Kim investigated the diastereofacially selective ring-closure reactions based on intramolecular ester enolate alkylation.[24] In most of the reactions, 3-substituted ester precursors were used as in reaction **18** → **19** (Scheme 3),[24a] where the $A^{1,3}$ strain influences the TS energy. The reaction **20** → **21** involves simple diastereoselection and dia-



Scheme 2. Examples of diastereofacially selective ring-closure reactions (part 1).

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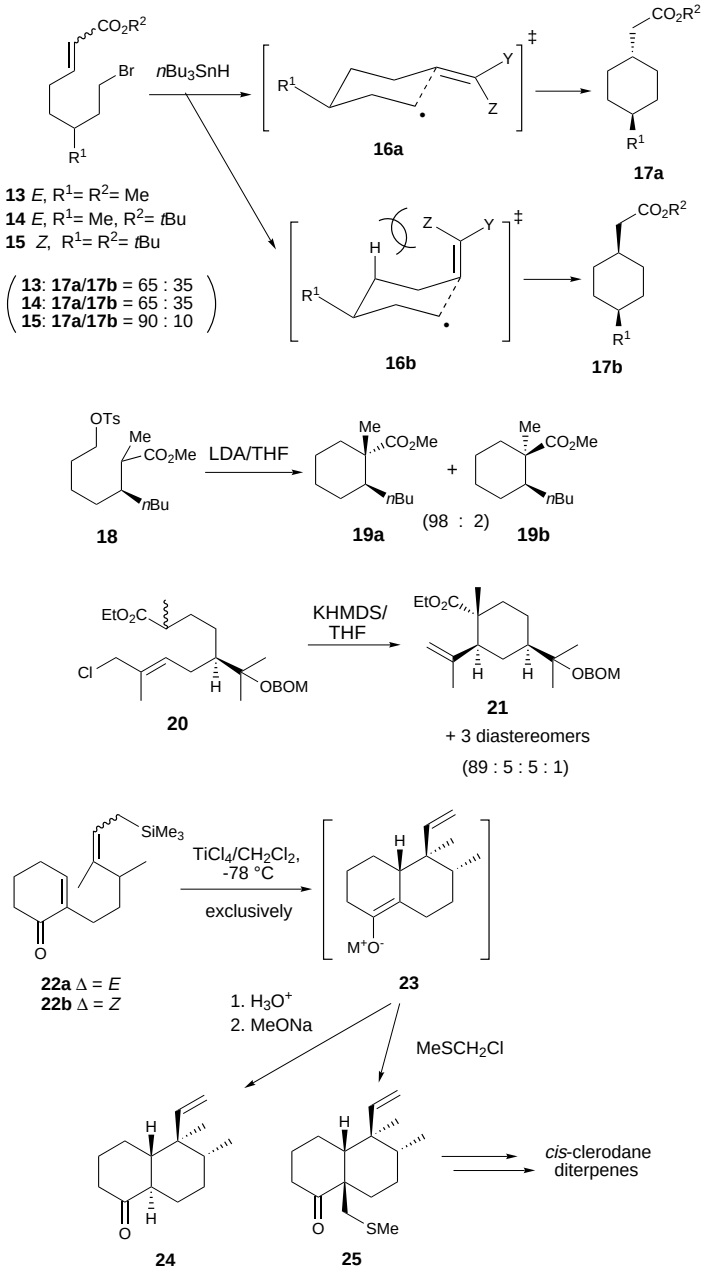
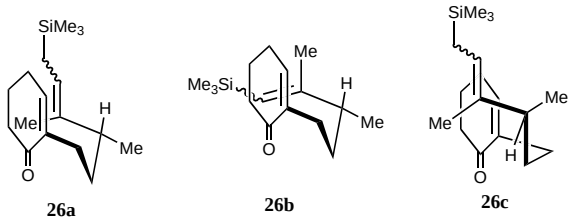


Scheme 3. Examples of diastereofacially selective ring-closure reactions (part 2).

stereofacial selection. In both cyclizations, the diastereofacial selection is explained in the same way as above on the grounds of the preference of the TS for an equatorial disposition of the substituent. The last example is a highly stereocontrolled cyclization **22**→**23**, which was developed by the author's group[9] in the course of studies on stereoselective synthesis of clerodane diterpenoids.[25] By alkyl trapping of the intermediate enolate **23**, one-pot stereoselective construction of a *cis*-clerodane skeleton like **25**, which has four contiguous stereogenic centers, was achieved,[26] the efficiency of stereocontrol being remarkably comparable to that of the Diels–Alder reaction. The stereochemical outcome involved—the simple diastereoselection and the diastereofacial selection—was rationalized in terms of orientation stereocontrol and folding-strain stereocontrol respectively (vide infra). This work gave us the incentive to investigate, especially, the latter subject further. Several examples described in this section would serve enough to demonstrate the potential of diastereofacially selective ring-closure reactions. References are given only for some other remarkable instances.[27]

Why folding-strain stereocontrol, and what is it? The issue of diastereocontrol in the conversion of **22**→**23** (Scheme 3) is discussed further here. The orientation stereocontrol would result from the preference for TS **26a** (with an antiperiplanar orientation) over TS **26b** (with a synclinal orientation) both for stereoelectronic and steric reasons, provided the TS is indeed chair-type. For the TS **26a**, a diastereomeric TS **26c** is conceivable with regard to the conformation of the secondary methyl group. Of these, **26c** would be energetically unfavorable because of the presence of the $A^{1,3}$ repulsion[15, 16] and



26a 26b 26c

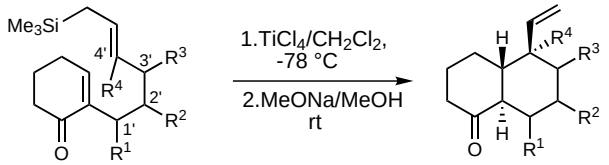
thus diastereoselective formation of the *cis*-dimethyl product **23** may be explained. However, this is not a sufficient explanation for the observed exclusive formation of **23** irrespective of double-bond geometry in **22**, since the allylic strain in the TS for the *E* substrate is estimated to be around 0.73 kcal mol^{-1} (≈4.73 kcal mol^{-1} for the *Z* substrate).[16,28] An additional factor which influences the relative energy balance between **26a** and **26c** is the gauche interaction. Since the secondary methyl groups in **26a** and **26c** adopt a *pseudo*-equatorial and a *pseudo*-axial conformation respectively, **26c** is subject to two additional gauche interactions that amount to ≈1.8 kcal mol^{-1}.[29] The energy difference of ≈2.53 kcal mol^{-1} in total would roughly account for the high diastereoselectivity experienced even for *E* substrate **22a**. Thus, the high diastereofacial selectivity experienced in cyclization **22**→**23** results from a combined effect of 1,3-allylic and gauche strains as observed in the IDA and the IE reactions of precursors with substituents attached at the carbon atoms next to dienophile and enophile groups, respectively.

Generally in the ring-closure reaction of an acyclic precursor with a stereogenic center on the chain, the diastereofacial selectivity may be rationalized by difference of the conformational energy (equatorial- versus axial-type disposition of the substituent) in the TS, while, in the case of the precursor with a stereogenic center at an allylic position, consideration should also be directed to stereoelectronic or torsional effects such as Felkin–Anh-type asymmetric induction[30] or $A^{1,3}$ strain, the concept of which has been refined through investigation of acyclic stereocontrol[3] in these last three decades. In the ring-closure reaction, disposition of the reacting groups is subject to conformational restriction, while new strain factors arise owing to the folding of the acyclic chain. Thus the strain energy difference between the diastereomeric foldings is decisive for the diastereoselectivity: the

selectivity between diastereomeric TSs (and thus diastereomeric products for thermodynamically controlled reactions) A and B is determined by the difference in the total sum of the strain energy involved (cf. Scheme 1). This viewpoint, implied by the term folding-strain stereocontrol, would permit basic and comprehensive reasoning about diastereofacial selection in ring-closure reactions, defining the difference from the intermolecular case.[31] There would exist various strain factors affecting the energy balance between the diastereomeric foldings—torsional strain, nonbonding interaction, allylic strain, electrostatic repulsion, and so on.[33] An energy difference of $\approx 2-3$ kcal mol^{-1} is sufficient to make a reaction diastereoselective, and folding-strain stereocontrol could be more effective than generally thought. While the kinds of atom (coordination number, bonding radius) constituting the ring[34] and the bulkiness of the substituent play an important role for the estimation of the conformational energy in the TS, the location of the stereogenic center relative to the reacting atoms should also be significant. The effect of a substituent on the steric energy could be altered delicately by its distance from the newly forming bond, which is longer than a normal bond. The conformational analysis of the cyclic TS (usually 5- and 6-membered) thus becomes a matter of pivotal concern. The total strain energy of a complex organic molecule, namely the steric energy, can be calculated by the molecular force-field method,[32] and recently its application to the TS in combination with molecular orbital calculations has also been explored.[35] With the development of this field, the prediction of the stereoselectivity on a quantitative basis will become a more general approach for synthetic chemists in the near future, while qualitative estimation of the steric energy through conformational analysis of diastereomeric cyclic TSs could be convenient for the design of diastereoselective cyclization reactions. For this purpose, it is important to estimate inclusively the strain energy involved.

Folding strain and remote diastereocontrol in ring-closure reactions: From the viewpoint of the folding-strain control delineated above, effective asymmetric induction could reasonably be expected in the ring-closure reaction of an acyclic substrate with a stereogenic center, even if it is remote from the bond-forming atom. Accordingly we investigated the diastereofacial selectivity in the cyclization of (*E*)-2-(6′-trimethylsilylhex-4′-enyl)cyclohex-2-enones **27**–**29** with alkyl substituents at various positions of the side chain,[10] which is related to the reaction described above (Scheme 3, **22**→**24**). The results are collected in Table 1. The cyclization of 1′-methyl-substituted substrates **27a** and **27b** showed low diastereoselectivity, probably because the energetic preference in the TS for an equatorial 1′-methyl group is counterbalanced by the *peri* interaction. The stereoselectivity was higher in the cyclization of 2′-methyl-substituted substrates **28a** and **28b**, being excellent for the latter (with a 4′-methyl group). In the reaction of 2′,3′-*anti*-dimethyl substrates **29a** and **29b**, in which the conformational effects of 2′- and 3′-methyl groups oppose each other, the diastereomeric preference of the products was reversed depending upon the presence of a 4′-methyl group. The result could be explained by the consideration that, in the cyclization of **29b**, the TS

Table 1. Diastereoselectivity in the ring closure reaction of (*E*)-2-(6′-trimethylsilylhex-4′-enyl)cyclohex-2-enones with alkyl groups at various positions in the side chain.



	R^1	R^2	R^3	R^4
27a	Me	H	H	H
27b	Me	H	H	Me
28a	H	Me	H	H
28b	H	Me	H	Me
29a	H	*anti*-Me	H	
29b	H	*anti*-Me	H	

	R^1	R^2	R^3
30	α-Me	H	H
31	β-Me	H	H
32	H	α-Me	H
33	H	β-Me	H
34	H	α-Me	α-Me
35	H	β-Me	β-Me

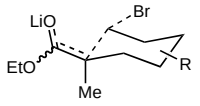
(**a**: R^4 = H; **b**: R^4 = Me)

Substrate	Yield [%]	Product diastereoselectivity Diastereomers	Ratio	δSE[d] [kcal mol^{-1}]
27a	79	**30a**/**31a**	1:1.8	1.13
27b[a]	75	**30b**/**31b**[b]	–	2.43
28a	47[c]	**32a**/**33a**	1:18.7	1.24
28b	45[c]	**32b**/**33b**	1:>500	3.54
29a	84[c]	**34a**/**35a**	6.9:1	−1.13
29b	83[c]	**34b**/**35b**	1:8.7	3.53

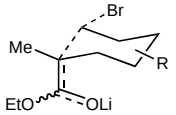
[a] *E*/*Z* = 7:1. [b] Complex mixture; analysis failed. [c] After treatment with NaOMe/MeOH. [d] Calculated by MM-2 for diastereomeric product enols.

with a *quasi*-axial 2′-methyl group would be decidedly disfavored by the presence of a severe nonbonding interaction with the 4′-methyl group. The differences in steric energy between the diastereomeric enol products calculated by MM-2 are listed in the right-hand column. Interestingly, the values correlate fairly well with the change in selectivity due to the introduction of a 4′-methyl group observed in the cyclization of **28** and **29**. This perhaps means that the reaction might proceed along the reaction coordinate while keeping a folding conformation similar to that of the product from a relatively early stage in the cyclization process.[36]

In order to investigate the problem further in a simpler system,[37] we selected the ring-closure reaction based on intramolecular ester enolate alkylation (cf. **8**→**9**)[12, 24a, 38] Four kinds of the 2-methyl containing substrates **36**–**39** with additional methyl substituents on various positions of the chain were prepared, and the diastereoselectivity in the reaction with LDA examined. As indicated in Table 2, the stereoselection associated with the folding-strain stereocontrol is fairly good except in the case of 5-substituted substrate **38**. Incidentally, *cis*- and *trans*-1,3-dimethylcyclohexanecarboxylates, **41b** and **41a**, were obtained stereodivergently by the respective choice of substrates, **37** and **39**. For the origin of the observed diastereoselectivity, we presume that, with respect to the disposition of the ester enolate grouping, the H-eclipsed conformation **43a** is more energetically favorable



43a



43b

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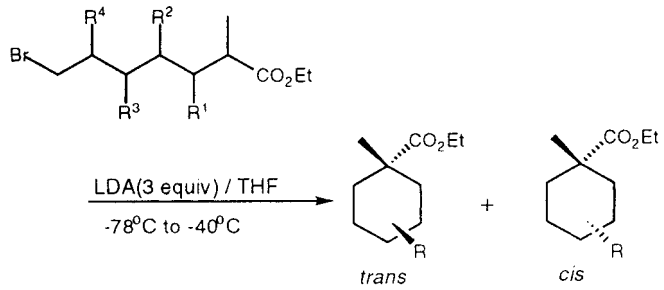
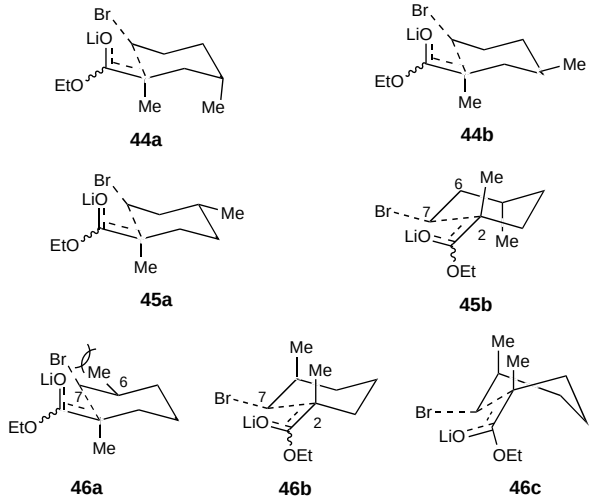
Table 2. Remote diastereocontrol in the cyclization of ethyl 7-bromo-2-methylheptanoates with a methyl group at various positions on the chain.



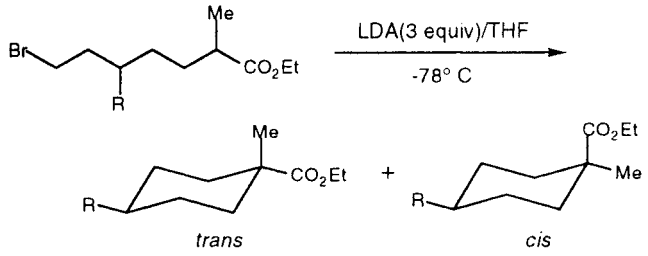
Substrate					Yield	Products	Ratio
R^1	R^2	R^3	R^4	[%]		*trans/cis*	
36	Me	H	H	H	78	**40a/40b**	96:4
37	H	Me	H	H	83	**41a/41b**	1:>99
38	H	H	Me	H	66	**42a/42b**	79:21
39	H	H	H	Me	53	**41a/41b**	93:7

than the bisected gauche form **43b**, as is assumed generally for an allylic system.[16,28] In support of this premise, a correlation between diastereofacial selectivity and bulkiness of the substituents was observed (vide infra).[39] The diastereoselection in the cyclization of **36** and **37** can be explained in a similar way to that described already. Two points remain to be clarified: 1) the lower selectivity in the cyclization of **38** than of **37** and 2) the origin of the selectivity for the cyclization of **39**. The rationale for the first result is that, in the cyclization of **37**, TS **44b** (leading to **41b**) would be decidedly preferred over TS **44a** (leading to diastereomer **41a**) because of the presence of a severe 1,3-diaxial methyl repulsion in the latter. However, the selectivity observed for the cyclization of **38** is lower than that predicted from the conformational energy of a methyl group ($\approx$1.8 kcal mol^{-1}). The decrease in the predominance of



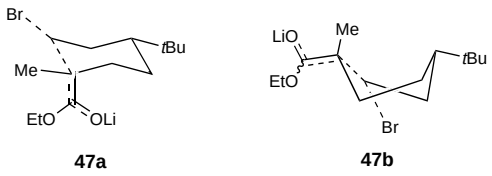
TS **45a** over TS **45b** might result from smaller additional gauche strain due to the axial methyl group, since one of the bonds (C6–C7) gauche to it in the TS **45b** might be less sterically constrained as a result of a loose and longer C2–C7 bond. As for the second point, TS **46b** involving 1,3-diaxial dimethyl repulsion has to be preferred over TS **46a**, which, at first sight, cannot be acceptable. However, in TS **46a**, a severe torsional strain would be present between the C6–methyl and the C7–bromine bonds, which are nearly synperiplanar. A tentative supposition is that the 1,3-diaxial dimethyl repulsion in the TS **46b** is not as strong as in a normal cyclohexane ring because the long C2–C7 bond intervenes between the carbon atoms bearing two methyl groups, the ultimate energy balance thus favoring TS **46b** or the related twist-boat form **46c**. From the viewpoint of folding-strain stereocontrol, a factor increasing the diastereoselectivity is the bulkiness of the substituents on the acyclic chain. This aspect was investigated in the cyclization of 5-substituted substrates in which the 5-methyl representative **38** showed only a moderate diastereoselectivity. The results are summarized in Table 3 with the relevant

Table 3. Effect of the bulkiness of the substituent on diastereoselectivity in the cyclization of 5-substituted 7-bromo-2-methylheptanoates.

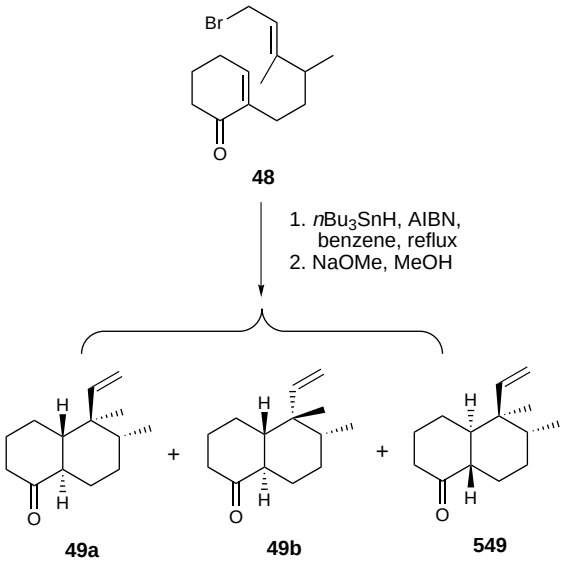


Substrate R	Diastereomeric products Yield [%]	Ratio *trans/cis*	A value [kcal mol^{-1}]
Me	66	79:21	1.8
Et	89	79:21	1.8
*i*Pr	85	86:14	2.1
*t*Bu	77	89:11	>4.5

conformational free energy (A value). Generally, the selectivity increased as the bulkiness of the 5-substituent increased, as anticipated. However, it is noteworthy that the diastereoselectivity for the cyclization of the 5-*tert*-butyl substrate was not as high as expected from the ability of the *tert*-butyl group to lock the cyclohexane conformation. The result might indicate the inadequacy of our chair-H-eclipsed model,[39] suggesting the intervention of a gauche TS **47a** or a twist-boat TS **47b**.

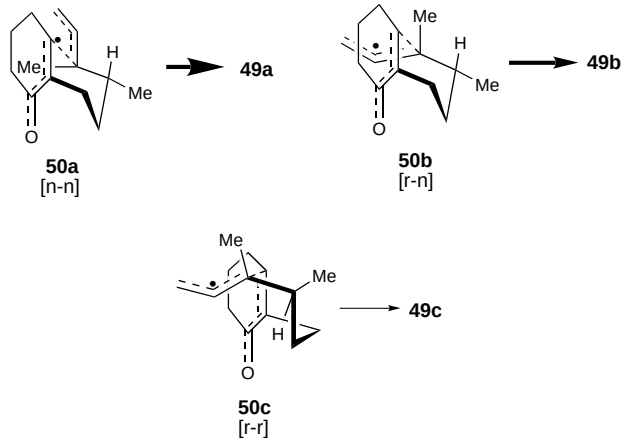


Reaction types and folding-strain stereocontrol: Comparison of the diastereofacial selectivity in the cyclization of different reaction types is intriguing with regard to the relationship between folding-strain stereocontrol and TS characteristics. With this in mind, radical and anionic versions of the highly diastereoselective cyclization **22**$\rightarrow$**23** were investigated.[40] Treatment of (*E*)-allylic bromide **48** with tri-*n*-butyltin hydride gave a mixture of three diastereomeric cyclization products **49a**, **49b**, and **49c** in a ratio of 77:21:2 (Scheme 4).[41]



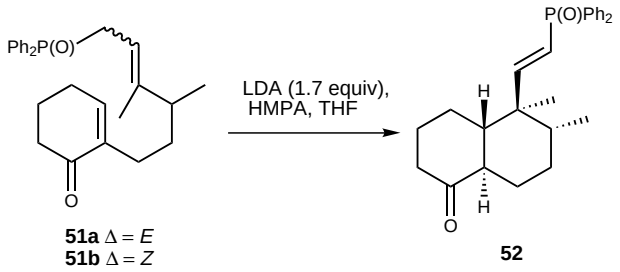
Scheme 4. A radical version of the ring-closure reaction **22**→**24**.

We interpret this result to indicate the preference of TSs in the order **50a** > **50b** > **50c**. The modes of cyclization in terms of the orientation and the folding-strain stereocontrols are normal – normal, reversed – normal, and reversed – reversed, respectively, as compared with those experienced in the cyclization **22**→**23** (Scheme 5). Thus, as far as folding-strain stereocontrol is concerned, the selectivity is as high as 98:2 (**50a**+**50b**:**50c**). This fact is notable in view of the early nature



Scheme 5. Diastereomeric foldings in TSs of radical cyclization **48**→**49**. The folding modes with respect to orientation and folding-strain stereocontrols are displayed in square brackets: n = normal, r = reversed.

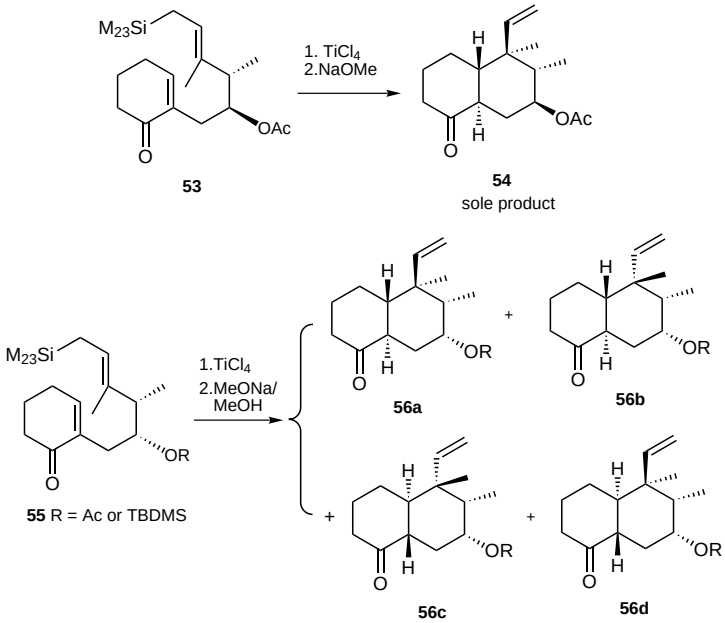
of the TS in radical reactions[20] and indicates that the major strain factors present in the product might be considerably developed from a relatively early stage in the chain folding leading to TS. The anionic cyclization of (*E*)- and (*Z*)-allylic phosphine oxides **51a** and **51b** was achieved, regioselectively and stereoselectively, by conducting the reaction at −40 °C and with HMPA as additive (Scheme 6). A single diastereomer **52** was



Scheme 6. An anionic version of the ring-closure reaction **22**→**24**.

obtained exclusively from both precursors, a high dual stereocontrol being comparable to the case of cyclization **22**→**23**. Thus, the folding-strain stereocontrol appears to be relatively unaffected with respect to the nature of the reactions concerned and, for the prediction of the diastereoselectivity, qualitative analysis based on the product-like TS would provide a practical guideline.

Alteration of cyclization modes by a controlling group: In the previous section, the original cyclization mode of substrate **22** to **24** as regards the diastereofacial selection was shown to be reversed by the presence of an additional methyl substituent at the 2′-position. If such a group can be removed at a later stage,[42] the cyclization might be used stereodivergently. This possibility was tested for oxy-substituted substrates.[43] Cyclization of *syn*-substrate **53** gave the 8,9-*cis*-dimethyl product **54** exclusively (Scheme 7) as anticipated on the grounds that both 2′-oxy and 3′-methyl groups would exert the conformational effect in the TS in the same direction. In contrast, the cyclization of the *anti* substrate **55** afforded a mixture of



stereocontrol	**56a**	**56b**	**56c**	**56d**
orientation	normal	reversed	normal	reversed
folding strain	normal	reversed	reversed	normal
R = Ac	7.7	1	2.4	—
R = TBDMS	4	1	2	2

Scheme 7. Alteration of cyclization modes in the reactions of *syn*- and *anti*-2′-oxy-substituted substrates.

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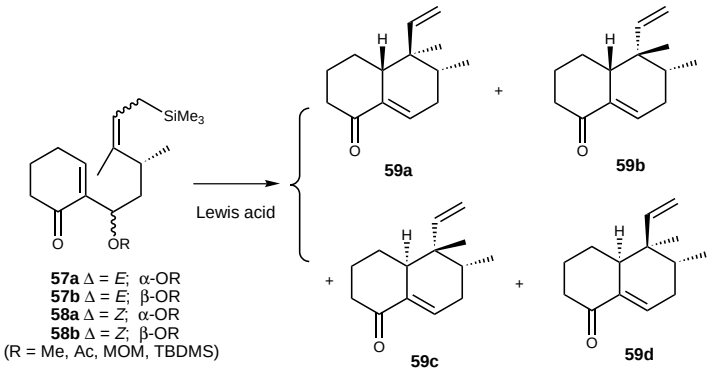
diastereomers under the combination of the dual stereocontrols in normal and reversed modes (Scheme 7). The reversal of the simple diastereoselection, as in the formation of **56b** and **56d**, might result from the loss in predominance of the antiperiplanar over synclinal alignment with respect to the disposition of two reacting π systems owing to intervention of the oxy substituents in coordination with the Lewis acid. Although the formation of cyclization product **56c** with 8,9-*trans*-dimethyl configuration desired for the natural product synthesis[44] was confirmed, the stereoselectivity remained too low to be synthetically useful. This result indicates that the steric energy difference between the diastereomeric TSs caused by the less bulky oxy substituents is not enough to make the reaction stereoselective. Eventually, alteration of the cyclization mode in a stereoselective manner was achieved by the use of 1′-oxy-substituted substrates **57** and **58** (Scheme 8).[43] Although the results of this work will not be detailed here, the cyclization reaction provides a method to obtain three diastereomeric octalone derivatives **59a**, **59c**, and **59d** out of four stereoselectively. The compounds **59a** and **59c** could be useful intermediates for the syntheses of 8,9-*cis*- and 8,9-*trans*-clerodane diterpenoids respectively.



Scheme 8. Lewis acid mediated cyclization of 1′-oxy-substituted substrates.

Conclusions

In a ring-closure reaction, the strain energy balance among the diastereomeric foldings—the folding strain—is determinative for the diastereofacial selectivity. Thus, in contrast to an intermolecular reaction, the diastereofacial selection could be sufficiently effective even in the cyclization of an acyclic substrate, the stereogenic center of which is located in a position remote from the reaction site, and is relatively unaffected by the type of reaction involved. Conformational analysis of the diastereomeric TSs is central for the estimation of the diastereofacial selectivity. In this regard, the interplay with approach by the MO force-field calculation will be extremely important. The design of diastereoselective ring-closure reactions based on the folding-strain stereocontrol concept is a useful approach in organic synthesis that deserves further extension to a wider range of reactions and substrates.

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