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Penultimate Group Effects in Free Radical Telomerizations of Acrylamides

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Abstract: *The telomerizaton of several acrylamides, most containing chiral auxiliary groups, was investigated. The first-formed stereogenic center in the n = 2 telomer (the penultimate center) has a significant effect on the configuration of the second (ultimate) center in the product. The penultimate chiral center of oxazolidine-derived acrylamides directs the configuration of the ultimate center such that the erythro n = 2 product is preferred. Sultam-substituted acrylamides preferentially lead, on the other hand, to threo products or give products with little stereoselectivity.*

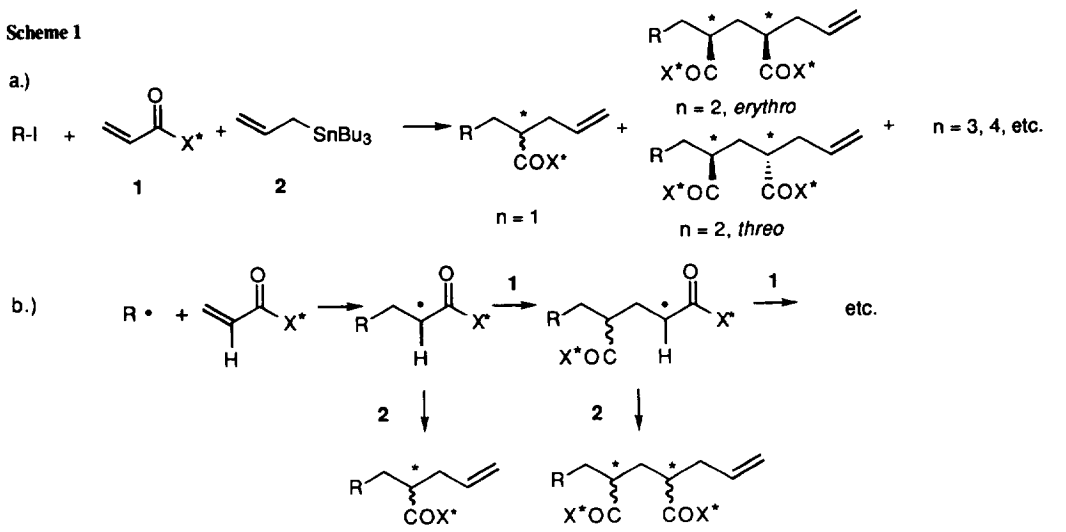
Rationally designed chiral auxiliaries can be used to control acyclic stereochemistry in free radical reactions.[1] Propagation sequences involving alkyl iodides, alkenes bearing chiral auxiliary groups, **1**, and allyl tributylstannane, **2**, have been used to determine the efficacy of auxiliary groups as stereocontrol elements, see Scheme 1a. Thus, allyl transfer reactions to the prochiral radical generated by addition of an alkyl radical to a vinyl monomer give products with a newly formed stereogenic center adjacent to the chiral auxiliary, see Scheme 1b. Effective chiral auxiliaries for such free radical reactions exert control of the configuration of the newly-formed center.

Chiral auxiliaries also have the potential to control the configuration of multiple stereogenic centers in iterative free radical additions including telomerizations and polymerizations. The synthesis of polymers of defined stereochemistry is, of course, a problem of commercial importance, and free radical methods generally fail to give significant stereochemical control. Additionally, the synthesis of natural products containing repeating subunits of defined stereochemistry could be achieved by using free radical methodology coupled with chiral auxiliaries.

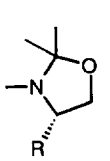
Among the several substructures that have been used as auxiliaries in free radical addition reactions, chiral amides are particularly effective. Addition reactions such as those shown in Scheme 1 have been investigated with auxiliary groups, X*, that include chiral oxazolidines, **3a** and **3b**,[2] and Oppolzer's sultam, **4**.[3] Oxazolidine **3a** and sultam **4** give n = 1 products with significant control of configuration of the new stereogenic center (25:1 and 10:1 respectively at 80 °C) while this product is formed with a selectivity of only 4:1 when the auxiliary group is **3b**. Despite the difference in stereocontrol exerted by auxiliaries **3a** and **3b** in simple allyl transfer reactions, polymers prepared from acrylamides bearing either **3a** or **3b** are formed with substantial control of stereochemistry. The *isotactic* structure is preferred, and *meso* (or *erythro*) diads are present in excess of 90% in polymers formed from acrylamides prepared from either auxiliary.[4] In contrast,

polymers derived from acrylamides bearing **4** are formed without control of stereochemistry.[5] The pattern of

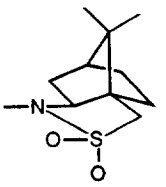
Scheme 1



stereoselectivity observed in the polymerizations is apparent after addition of only two monomers, as evidenced by the diastereomeric ratios of the n = 2 products formed from the chiral acrylamides. The *erythro* diastereomer is the dominant n = 2 product formed from the acrylamide bearing oxazolidine **3b** while n = 2 products derived from the Oppolzer acrylamide are formed with little selectivity.[6]



***S*-3a**, R = ^{t}Bu
***S*-3b**, R = ^{i}Pr
3c, R =H



***S*-4**

The first-formed stereogenic center clearly plays an important role in influencing the selectivity of the second center formed in the sequence, so there is an interplay between the influence of the auxiliary group and that of the penultimate center in determining the stereochemical outcome of the allyl transfer reaction. In order to provide an understanding of this effect, we have studied the selectivity of several addition reactions that lead to n = 2 products, and we report here the results of these studies.

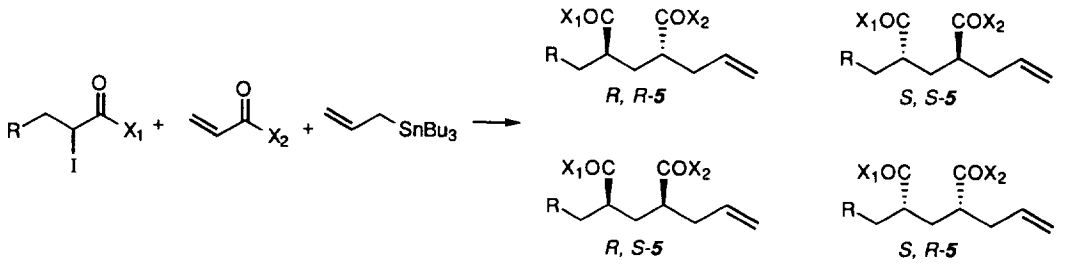
RESULTS

Two strategies were used to examine the interplay of the auxiliary group and the penultimate stereogenic center in radical addition. The direct approach involved reaction of an alkyl iodide, an acrylate substituted with

the auxiliary group, and allyl tributylstannane, as illustrated in Scheme 1a. Alternatively, an alkyl iodide bearing an auxiliary was reacted with an acrylate derivative and allyl tributylstannane to give the n = 2 compounds.

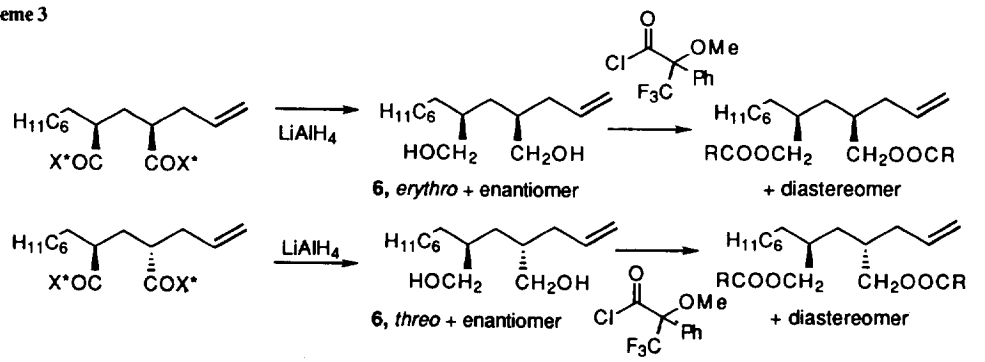
This second approach, illustrated in Scheme 2, offers the advantage that different auxiliary groups can be substituted on the penultimate and ultimate centers, allowing a diverse set of reactions to be examined. Furthermore, with this approach, conditions can be manipulated such that the n=2 products can be obtained in yields of 60-70%. The telomerization approach, on the other hand, gives significant amounts of higher telomers with the n=2 products never being more than 30% of the product mixture.

Scheme 2



The n = 2 products, **5**, formed by these procedures contain two stereogenic centers, thus four stereoisomeric products are produced in the addition reactions (enantiomeric *threo* and *erythro* compounds when $X_1 = X_2$ is achiral, four diastereomers as shown in Scheme 2 when X_1 or X_2 is chiral and optically pure). In some instances, the four products were separated directly by gas chromatography. For most of the product mixtures this was not possible, however, and derivatization procedures were required to provide complete analyses. Several procedures were developed for the purpose of determining the ratios of these four products. One strategy (Method A) involved hydrolysis of the C(O)X groups and conversion of the resulting dicarboxylic acids, *via* the diacid chlorides, to the bis-amides of *(S)*-[–]-α-methylbenzyl amine. The four diastereomers of

Scheme 3



this bis-amide separate directly by gas chromatography and their stereochemical configurations have been assigned.[7] It was established that kinetic resolution does not complicate this analysis in those systems that could be analyzed directly. A comparison of the results obtained by derivatization and by direct analysis was always within a few percent. A small amount of epimerization apparently does attend this sequence of reactions however, and the results obtained appear to overestimate the amount of minor stereoisomeric products in the reaction mixture. Stereoselectivities reported by the derivatization analytical method may therefore be underestimated by a few percent.

Amides derived from **4** or analogous sultams reduce to substituted methanols upon reaction with lithium aluminum hydride (LAH). Thus the n = 2 products derived from sultam acrylamides are reduced to the bis-methanols **6**, which are converted to diastereomeric esters by reaction with Mosher's acid chloride, see Scheme 3. Analysis of the ^{19}F NMR spectrum of the Mosher esters gives infomation about the enantiomeric purity of the precursor **6**. An analysis of the *threo/erythro* diastereomer ratio by gas chromatography coupled with analysis of Mosher esters formed from the separated diastereomers **6** gives a complete report of the stereoisomeric product composition. This method (Method B) gives analyses ±5% due to partial overlapping of some resonances in the ^{19}F NMR spectra.

In Table 1 are presented the product compositions for the n = 2 products, **5**, formed in benzene at 80° C for reactions of cyclohexyl iodide or alkyl iodide bearing an auxiliary with various alkenes by the sequences shown in Schemes 1 and 2. Addition reactions were carried out with various concentrations of alkyl iodide, alkene, and allyl tributylstannane, and the distribution of n = 2 products was determined to be independent of the concentrations of these reactants.

Table 1. n=2 Product Composition vs. Auxiliary Group at 80° C[a]

Entry	Reaction Scheme	X_1	X_2	Method of Analysis	*R,R*-5	*R,S*-5	*S,S*-5	*S,R*-5
1	Scheme 1	OMe	OMe	A	30	21	29	20
2	Scheme 2	OMe	*S*-**3b**	A	18	37	37	8
3	Scheme 2	*S*-**3b**	OMe	A	53	37	6	4
4	Scheme 1	*S*-**3b**	*S*-**3b**	A	10	78	9.4	2.6
5	Scheme 2	*S*-**3b**	*R*-**3b**	A	25	59	3	13
6	Scheme 2	*S*-**3b**	**3c**	A	24	58	6	12
7	Scheme 1	*S*-**4**	*S*-**4**	B	36	46	10	8
8	Scheme 2	*S*-**4**	*R*-**4**	B	71	13	12	4
9	Scheme 2	OMe	*S*-**4**	B	12	40	8	40

a. R,= cyclohexyl, X_1, X_2 are as indicated in Schemes 1 and 2. Analytical methods A and B are described in the text.

Table 2 presents the composition of the n = 2 products formed in the addition of the neopentyl radical to the acrylamide *S*-**3b**. All four n = 2 products, **5**, formed in this addition separate completely by gas chromatography. The analysis of this product mixture can therefore be achieved without derivatization. The products formed from the addition of neopentyl radical to *S*-**3b** were prepared independently by the use of Evan's titanium enolate chemistry[8] by following a strategy analogous to that used previously to determine the

absolute configuration of bis-phenethylamide n = 2 products.[7] The elution order on a 30 m SPB-5 capillary column of the diastereomers was *S,S*-**5**, *R,R*-**5**, *R,S*-**5**, and *S,R*-**5** .

The telomerization of the achiral acrylamides **7-10** was also investigated. The products for these achiral monomers consist of a mixture of racemic *threo* and *erythro* diastereomers, and the configurations of these products were identified by correlation with known n = 2 products. In most cases the *threo* and *erythro* products separated directly by gas chromatography and silica gel chromatography. The sultam products (Table

Table 2. Temperature Dependence of n=2 Product Composition for Addition of Neopentyl Radical to Acrylamide *S*-3b.[a]

Entry	T (K)	*R,R*-5	*R,S*-5	*S,S*-5	*S,R*-5
1	273	6.7	89.0	3.8	0.5
2	313	7.6	86.4	4.9	1.1
3	333	7.9	85.3	5.4	1.4
4	353	8.4	83.7	6.1	1.8
5	405	9.3	79.3	8.3	3.1

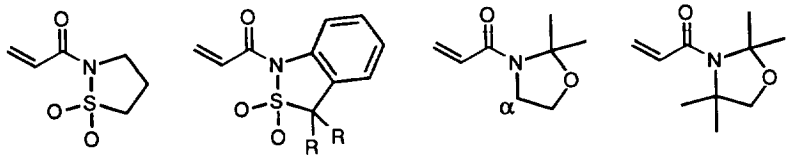
a. Reactions were carried out in benzene: 100 mM neopentyl iodide, 100 mM oxazolidine acrylamide, 300 mM allyl tributylstannane. Product mixtures were analyzed on a 30 m SPB-5 column (220°C isothermal), direct analysis.

Table 3. *Threo/Erythro* Product Composition for Telomerization of Alkenes 7-10.[a]

Alkene	T (K)	Solvent	*Threo*	*Erythro*
7[b]	273	Ph-Cl	82.7	17.3
7[b]	313	Ph-Cl	78.2	21.8
7[b]	333	Ph-Cl	74.8	25.2
7[b]	405	Ph-Cl	71.0	29.0
7	313	Ph-CH_3	80	20
7	313	Dioxane	75	25
7	313	CH_2Cl_2	80	20
7	313	EtOH	77	23
7	313	CH_2Cl_2/CH_3CN	69	31
8a	333	Ph-H	67	33
8b	333	Ph-H	71	29
8c	333	Ph-H	73	27
9	333	Ph-H	60	40
10	333	Ph-H	35	65

a. Reactions were carried out with 100 mM cyclohexyl iodide, 100 mM acrylamide, 300 mM allyl tributylstannane. b. Average of triplicate analyses of duplicate runs.

3, **8a-c**) were analyzed by lithium aluminum hydride reduction and gc analysis of the resulting diols. The product distribution of n = 2 products for reaction of cyclohexyl iodide with the alkenes **7-10** is presented in Table 3.

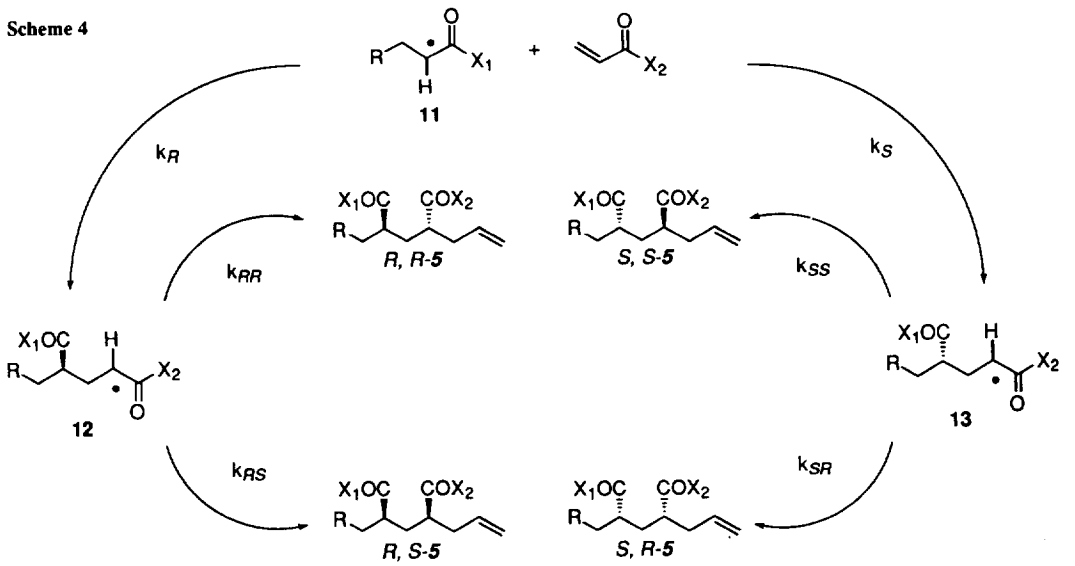


7 **8** **a, R=H** **b, R=Me** **c, R=Ph** **9** **10**

DISCUSSION

In the addition sequence leading to n = 2 products, the configuration of the two stereogenic centers is established in two serial steps, as shown in Scheme 4. The data reported in Tables 1-3 can be analyzed on the basis of the selectivity of the serial additions. Consider the data for Table 1, entry 4, as an example. The

Scheme 4



selectivity for the first addition reaction, k_R/k_S is determined by the product ratio $(RR + RS)/(SR + SS)$ = 88/12. The selectivities for the second addition steps can also be extracted from the product mixture and for the

reaction in Table 1, entry 4, k_{RS}/k_{RR} = (*RS/RR*) = 78/10 = 89/11, while k_{SS}/k_{SR} = (*SS/SR*) = 9.4/2.6 = 79/21. As expected from auxiliary control,[1] the *(S)*-**3b** auxiliary leads preferentially to the *R* configuration at the first center formed and favors formation of the *S* configuration at the second center. This analysis shows that the selectivity for addition of amide-substituted radicals **11** bearing the *(S)*-**3b** oxazolidine auxiliary to acrylamides bearing the same auxiliary group proceeds with selectivity higher than reaction of the same radicals with allyl tributylstannane. At 80° C, radical **11** having X_1 = *(S)*-**3b** reacts with allyl tributylstannane with a selectivity of 4/1 while the same radical reacts with electron deficient alkenes (X_2 in Table 1) with a selectivity of ~9/1. The stereocontrol exerted by the auxiliary group depends to some degree on the structure of the alkene radical trap. Values of k_R/k_S, k_{RS}/k_{RR}, and k_{SS}/k_{SR} determined for reactions of radicals bearing various X_1 and X_2 groups are presented in Table 4.

The penultimate center affects the selectivity of the allyl transfer reaction. Thus, radical **12** having X_1 = X_2 = *(S)*-**3b** reacts with allyl tributylstannane with a selectivity of 9/1, higher than the 4/1 selectivity observed for reaction of the corresponding radicals **11** or **13** with allyl tributylstannane. An even more dramatic effect of the penultimate center is seen in the experiment corresponding to entry 5 in Tables 1 and 4 in which X_1 = *(S)*-**3b** and X_2 = *(R)*-**3b**. If auxiliary control operated in each of the serial steps, the *(S)*-**3b** auxiliary would favor the *R* configuration at the first center, the *(R)*-**3b** auxiliary would favor the *R* configuration at the second center, and the *threo* (*R,R*) diastereomer would predominate. The *R* configuration is indeed favored at the first center, the product ratio (*RR* + *RS*)/(*SR* + *SS*) = 84/16. However, the selectivities for the second addition steps are: k_{RS}/k_{RR} = 70/30, and k_{SS}/k_{SR} = 19/81. The configuration of the new stereogenic center formed in the allyl transfer to radical **12** is not controlled by the auxiliary group in the expected manner—the "wrong" (*erythro*) diastereomer is the favored product in this addition. In contrast, allyl transfer to the diastereomeric radical **13**

Table 4. Competition Rate Constants for Radical Additions Described in Scheme 4.

Entry	X_1	X_2	k_R/k_S	k_{RS}/k_{RR}	k_{SS}/k_{SR}
1	OMe	OMe	52/48[a]	40/60	59/41
2	OMe	*S*-**3b**	55/45[a]	67/33	82/18
3	*S*-**3b**	OMe	90/10	40/60	60/40
4	*S*-**3b**	*S*-**3b**	88/12	89/11	79/21
5	*S*-**3b**	*R*-**3b**	84/16	70/30	19/81
6	*S*-**3b**	**3c**	81/19	70/30	32/68
7	*S*-**4**	*S*-**4**	82/18	56/44	55/45
8	*S*-**4**	*R*-**4**	84/16	15/85	75/25
9	OMe	*S*-**4**	52/48[a]	77/23	17/83

a. Values determined by experiment, this ratio is required to be 50/50.

proceeds by normal auxiliary control to give the *S,R* product. These findings illustrate a possible limitation of chiral auxiliaries in radical additions. Chiral auxiliaries have been used successfully in radical addition reactions to acheive stereocontrol in single additions and in the formation of *erythro* 1,3-stereocenters (*isotactic* polymers). However, the present results suggest that the chiral auxiliary strategy cannot be directly used to generate a *threo* arrangement of 1,3-stereocenters due to the effect of the penultimate center.[9]

The experiments with the sultams also provide an interesting case study in how the penultimate effect can be modulated by the pairing of substituents. Radical **12** derived from X_1 = OMe, X_2 = *S*-**4** (Tables 1 and 4, entry 9) gives a ratio (77/23) close to that predicted by multiplying the expected facial selectivity for Oppolzer's sultam (about 9/1) by the penultimate effect (about 0.5) of the achiral models reported in Table 3. Not surprisingly, a similar ratio of products is seen for radical **13**, which in this case is the enantiomer of **12**. For radical **12** when the two auxiliaries are the same enantiomer ($X_1 = X_2$ = *S*-**4**, Tables 1 and 4, entry 7), the selectivity is lower than expected (56/44) by simple multiplication, though the auxiliary still controls. This predicts a matching of effects for radical **12** when the two auxiliaries are the opposite enantiomer (X_1 = *S*-**4**, X_2 = *R*-**4**). This radical does indeed give the highest *threo* selectivity of the study (84/16); however, this ratio is still only about the level expected for the auxiliary itself. The expected "bonus" of the penultimate effect and the "mis-matching" of the auxiliaries is not observed. Discussion of trends for radicals **13** from the two chiral sultam pairings is probably not warranted given the analytical limits and the fact that the ratios of two minor products are compared.

The temperature–selectivity study reported in Table 2 provides information about enthalpies and entropies of activation of competing transition states for telomerization of acrylamide *(S)*-**3b**. Eyring analysis of these data provides $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ for the competing transition states for each of the three selective reactions in the serial sequence. Thus, for the reaction of radical **11**, k_R/k_S, $\Delta\Delta H^{\ddagger} = -7.4 \pm 0.4$ kJ mol^{-1} and $\Delta\Delta S^{\ddagger} = -0.9 \pm 1.3$ J K^{-1} mol^{-1}. The selectivity is enthalpy driven, and the entropy term is close to zero.

For the competition corresponding to the reaction of radical **12** with allyl tributylstannane, k_{RS}/k_{RR}, $\Delta\Delta H^{\ddagger} = -2.9 \pm 0.2$ kJ mol^{-1} and $\Delta\Delta S^{\ddagger} = 10.8 \pm 0.7$ J K^{-1} mol^{-1}. Enthalpy and entropy contribute to the selectivity in this case though the enthalpy effect is substantially smaller than that observed in the reaction of **11**. Both enthalpy and entropy favor the *erythro* product in the reactions of radical **12**. The competition corresponding to the reaction of radical **13** with allyl tributylstannane, k_{SS}/k_{SR}, gives $\Delta\Delta H^{\ddagger} = -6.3 \pm 0.9$ kJ mol^{-1} and $\Delta\Delta S^{\ddagger} = -7.9 \pm 2.5$ J K^{-1} mol^{-1}. Both enthalpy and entropy again contribute to the selectivity in this case, but here enthalpy favors the *threo* product and entropy favors the *erythro* product.

A temperature—selectivity study was also carried out for the achiral sultam–acrylamide **7**, see Table 3. Here there is only one diastereoselective step, $k_{threo}/k_{erythro}$, and an Eyring analysis gives $\Delta\Delta H^{\ddagger} = -4.7 \pm 0.3$ kJ mol^{-1} and $\Delta\Delta S^{\ddagger} = -4.1 \pm 0.9$ J K^{-1} mol^{-1}. Both enthalpy and entropy contribute to the selectivity in this case and here again enthalpy favors the *threo* product and entropy favors the *erythro* product.

While the penultimate group may appear to exert a significant influence on the stereoselectivity in telomerizations, in most cases the actual effect represents a small energetic difference in competing transition states, < 8 kJ mol^{-1}. Given the conformational flexibility of intermediate radicals such as **12** and **13**, it seems unlikely that a comprehensive theory can be developed to explain our data. Nevertheless, we analyze the problem based on precedents of methacrylate polymerization and telomerization[9] in order to formulate a working hypothesis to aid in making generalizations and predictions. Figure 1 presents four reasonable conformations of radical **12**. These conformations are based upon EPR studies on analogous radicals that indicate a preference for the orientation about the radical with the C_2-C_3 β bond eclipsing the radical orbital.[11] Interconversion of conformers A ⇌ B and C ⇌ D occurs by rotation about the C_2-C_3 bond while conformers A ⇌ C and B ⇌ D interconvert by rotation about the C_3-C_4 bond. Conformer A has the CH_2R chain *anti* to the radical

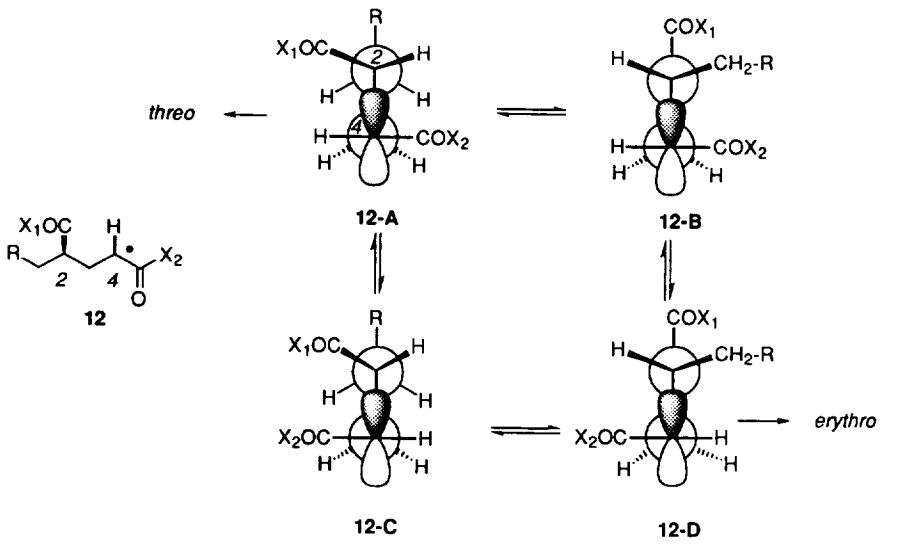


Figure 1. Conformations of Radical 12.

with the other groups on C_2 and C_4 arranged to minimize 1-3 steric interactions.[10] Conformer C has the CH_2R chain *anti* to the radical but the COX_1 and COX_2 groups are eclipsed. Conformers **B** and **D** have the COX_1 group *anti* to the radical and for this pair the **B** radical has the CH_2R and COX_2 groups eclipsed. Because of these eclipsing interactions, we suggest that conformers **12A** and **12D** are lower energy than **B** and **C**. We also suggest that in most cases these 1,3 eclipsing steric interactions will be minimized in the transition states resulting from conformers **12A** and **12D**.

The bottom face of radicals **12A-D** is open for reaction while the top face is shielded by the penultimate center. Reaction of each of these radicals will therefore preferentially occur from the bottom face: the *threo* product will predominate upon reaction from conformers **12A** and **12B**, and the *erythro* diastereomer will predominate upon reaction from conformers **12C** and **12D**. We have identified radicals **12A** and **12D** (along with their associated transition states) as being the important conformers in discussions of radical selectivity and this, coupled with the argument concerning the **12A-D** facial selectivity, suggests that the penultimate effect is determined by the relative energy of transition states derived from conformer **12A** (giving the *threo* product) and **12D** (that gives the *erythro* product). Substituents at the penultimate center, *i.e.* the X_1 group, may influence the population of confomers **12A** and **12D** and in this way provide a *threo* or *erythro* bias in the allyl transfer reaction.[5] Sultam substituents at the penultimate center (derived from **7-8**) lead preferentially to the *threo* product, hence the transition state derived from conformer **12A** is favored. Oxazolidines give either *threo* or *erythro* products depending upon whether there is substitution at the α position (see structure **9**). Thus **9** gives the *threo* product while **10**, having dimethyl substitution at the C-4 position, gives the *erythro* product preferentially.

Superimposed on the penultimate group effect is, of course, the effect of the auxiliary group. In some cases, the penultimate and auxiliary effects will be matched while in other cases the effects will oppose one another. The results presented in Tables 1-2 can, for the most part, be understood on this basis. Oxazolidines

substituted at the α position react with a penultimate *erythro* preference. In the case where $X_1 = X_2 = (S)$-**3b**, the auxiliary group and the penultimate center are matched, they both favor the *erythro* product (i.e., both the auxiliary X_2 and the penultimate center shield the top face in conformer **12D**). Sultams, on the other hand, react with a penultimate *threo* preference. In the case where $X_1 = X_2 = (S)$-**4**, the auxiliary group and the penultimate center are mismatched (that is, the auxiliary X_2 shields the bottom face and the penultimate center shields the top face in conformer **12A**). The auxiliary effect dominates but the selectivity is significantly reduced. (Compare the ratios of *R,S* to *R,R* diastereomers for entries 8 and 4 in Table 1.)

A small solvent polarity effect is observed for the *threo/erythro* selectivities determined for the sultam **7**. Thus, reaction in toluene gives a 4/1 *threo/erythro* ratio while ethanol/acetonitrile solvent mixtures give product with a *threo/erythro* ratio of ~2/1. This effect may be ascribed to a favorable interaction of the sultam S—>O dipoles on the penultimate and ultimate centers in the transition state corresponding to conformation **12A**. A similar solvent polarity effect has been observed for telomerizations of achiral oxazolidinones.[9] This dipole-dipole stabilizing interaction favors the *threo* product arrangement for oxazolidinones or sultam. The penultimate group for these substituents therefore naturally opposes the auxiliary imposed *erythro* bias.

Most of the results in Tables 1-3 can be rationalized by our working hypothesis. A few notable exceptions exist that are worth mentioning. The penultimate effect has been treated as a perturbation, either enhancing or diminishing the selectivity due to the auxiliary. However, the interplay between these two effects appears to be dependent, to some extent, on the structure of the groups in both the penultimate and ultimate positions (X_1 and X_2). In the case where $X_1 = (S)$-**3b** and $X_2 = (R)$-**3b** (Table 1, entry 5), the penultimate and auxiliary effects oppose one another but the penultimate effect dominates.[12]

It has been assumed that the population of reactive conformers **12A** and **12D** in Figure 1 is controlled by the structure of the penultimate group (X_1). Comparison of two examples which differ only in the identity of X_2 suggests that the group in the ultimate position also influences the population of these conformers. When $X_1 =$ (*S*)-**3b** and $X_2 =$ **3c** (Table 1, entry 6) the penultimate effect favors the *erythro* product as expected for α substituted oxazolidines. When $X_2 =$ OMe (Table 1, entry 3) the penultimate effect favors the *threo* product.

In summary, the penultimate group may exert a substantial effect in auxiliary-controlled free radical telomerizations. Penultimate oxazolidines bearing substitutents in the α position favor additions leading to *erythro* diads. This *erythro* bias appears to be entropy controlled. Sultam auxiliary groups on the penultimate center, on the other hand, favor *threo* diads enthalpically.

EXPERIMENTAL

General Procedures

Cyclohexyl iodide, neopentyl iodide and allyl tributylstannane were obtained from Aldrich and used without further purification. Methyl acrylate obtained from Aldrich contained hydroquinone monomethyl ether as a stabilizer and was passed through an inhibitor removal column prior to use. AIBN was recrystallized from ethanol. ^{1}H NMR spectra were obtained on a Varian XL-300. IR spectra were obtained on a Bomem Michelson Series BM-100 FTIR spectrophotometer using $CHCl_3$ as solvent. Mass spectra were obtained on a Hewlett-Packard 5988A gas chromatagraph/VG-ZAB 1F spectrometer using methane/ammonia for chemical

ionization. Gas chromatograms were recorded on a Hewlett-Packard 3393A gas chromatagraph under one of the following conditions: 15 m x 0.32 mm i.d. SPB-1 column at 5 psi with 280°C injection port temperature or 30 m x 0.32 mm i.d. SPB-5 column at 15 psi with 280°C injection port temperature.

***S*-3b** and its acrylamide as well as ***R*-3b** and its acrylamide were prepared and described as in ref 2.

2,2-Dimethyl-1,3-oxazolidine, 3c.[13]

A flame dried flask was charged with 25.0 mL (0.414 moles) of ethanolamine (Aldrich, 99+%) and 150 mL of dry acetone. The solution was stirred under an atmosphere of argon for 3 h at room temperature then diluted with 350 mL of dry CH_2Cl_2 and 90 g of anhydrous $MgSO_4$ was added. The mixture was stirred overnight at room temperature. The $MgSO_4$ was removed by filtration and washed thoroughly with CH_2Cl_2. The filtrate was concentrated in vacuo to give 29.7 g of clear, colorless oil (71%) which was stored in the dark under an atmosphere of argon. The mixture contained both the desired oxazolidine and the imine which codistilled. The mixture was carried on without further purification. ^1H NMR (C_6D_6) oxazolidine: δ 3.5 (2H, t), 2.7 (2H, t), 1.2 (6H, s). imine: δ 3.9 (2H, t), 3.2 (br, 2H), 1.8 (s, 3H), 1.3 (s, 3H).

Acrylic 2,2-dimethyl-1,3-oxazolidinide, 9.

A flame dried flask was charged with 10.0 g (98.9 mmoles) of 2,2-dimethyl-1,3-oxazolidine and 200 mL dry THF. The flask was purged with argon and cooled to 0°C. Triethylamine (distilled over KOH), 13.8 mL (99.0 mmoles) was added dropwise followed by a solution of 8.2 mL (98.9 mmoles) acryloyl chloride in 20 mL dry THF. The solution was stirred for 1 h at 0°C then 30 min at room temperature. The reaction mixture was concentrated in vacuo. The resulting residue was dissolved in ether and washed with 20 mL of d H_2O, 20 mL saturated $NaHCO_3$ and 20 mL saturated brine solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a yellow oil. Vacuum distillation (bp=55°C/3 torr mm Hg) afforded 2.1 g of clear, colorless oil (14%). A significant portion of the product is believed to have beeen lost during the workup due to its partial water solubility: ^1H NMR (C_6D_6) δ 6.4 (1H, m), 6.1 (1H, m), 5.3 (1H, m), 3.5 (2H, t), 3.0 (2H, t), 1.4 (6H, s); ^{13}C NMR (C_6D_6) δ 162, 130, 127, 95, 63, 46, 25; MS *m/e* 169 (M^+), 150, 142, 104, 78; HRMS calc for $C_7H_{10}NO_2$ ($M^+ - CH_3$) 140.0715, found 140.0705.

Oppolzer's S-camphor sultam and its acrylamide, and **Oppolzer's R-camphor sultam** and its acrylamide, were prepared described as in ref 3b.

1,3-Propanesultam acrylamide, 7.

A 250 mL round bottom flask was cooled to 0°C, charged with 100 mL THF, 1.0 g (8.3 mmoles, 1eq) of 1,3-propane sultam[14] and 0.7 g (approx 2 eq) of a NaH in a 60% suspension in mineral oil (washed with benzene before use) and stirred for 1 h after which 1.0 mL (9.9 mmoles, 1.2 eq) 3-bromopropionyl chloride was added dropwise. The mixture was stirred for 30min at 0°C and 1 hour at room temperature before being diluted with 100 mL ether and washed with 50 mL saturated NH_4Cl solution. The organic extract was poured into a 500 mL round bottom to which 36 mL triethylamine (258 mmoles) was added and stirred for four hours. The mixture was washed with 1/1 solution of 1N HCl and saturated NH_4Cl solution, dried with $MgSO_4$, filtered and concentrated. The crude residue was chromatographed on silica with 200mL 50% ethyl acetate in hexane and then with pure ethyl acetate until product eluted to give 529 mg (3.02 mmoles, 37% yield) of a pale yellow solid. ^1H NMR ($CDCl_3$) δ 6.9 (1H, m), 6.5 (1H, m), 5.9 (2H, m), 3.9 (2H, t), 3.45 (2H, t), 2.4 (2H, t). ^{13}C NMR ($CDCl_3$)- δ 163, 131, 127, 50, 44, 18. GCMS (CI, CH_4/NH_3) *m/e* 175 (MH^+), 193 ($M+NH_4$). HRMS calc for $C_6H_9NO_3S$ (M^+) 175.0303, found 175.0306.

3,3-Dihydro-1,2-benzisothiazole-1,1-dioxide.

To a THF solution (100 mL) of saccharin (5 g, 27.3 mmol) stirring at room temperature was added $LiAlH_4$ (2.18 g, 54.6 mmol). The mixture was stirred at room temperature for 1 h then cooled to 0°C and diluted with ethyl acetate (100 mL). Water (0.55 mL) was added followed by 5% HCl (0.55 mL), then saturated NH_4Cl (1.5 mL). The mixture was filtered through celite to remove aluminum salts. Concentration of the filtrate provided 3.07 g (66% yield) of the sultam, mp 98-100°C. ^1H NMR (d_6- acetone) δ 7.77 (1H, d, J = 7.6 Hz), 7.66 (1H, d, J = 7.7 Hz), 7.58 (2H, t, J = 7.7 Hz), 4.52 (2H, s), 2.90 (1H, broad s); ^{13}C NMR (d_6- acetone) δ 138.6, 137.1, 133.3, 129.5, 125.8, 121.1, 45.8; IR (neat) 3217, 1393, 1279, 1157, 1125, 735 cm^{-1}; MS *m/e* 169 (M^+), 150, 142, 104, 78; HRMS calc for $C_7H_7NO_2S$ 169.0198 found, 169.0201.

3,3-Dihydro-2-(1-oxo-2-propenyl)-1,2-benzisothiazole-1,1-dioxide, 8a.

To a suspension of sodium hydride (520 mg of a 60% dispersion, 13.0 mmol) in THF (40 mL) at room temperature under a nitrogen atmosphere was added a THF solution (10 mL) of the above sultam (2 g, 11.8 mmol) dropwise. After 1 h a THF solution (10 mL) of 3-chloropropionylchloride was added. The mixture was stirred an additional 1 h, and excess triethylamine was added. The reaction mixture was allowed to stir 1 h, and then was washed with 1 N HCl and bicarbonate solution (each 2 x 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes/ethyl acetate, 5:1) afforded 1.87 g (71% yield) of **8a**, mp 134-136°C. ^1H NMR ($CDCl_3$) δ 7.8 (1H, d, J = 7.9 Hz), 7.7 (1H, t, J = 6.8 Hz), 7.6 (1H, t, J = 7.3 Hz), 7.5 (1H, d, J = 7.8 Hz), 7.1 (1H, dd, J = 10.3, 18 Hz), 6.6 (1H, dd, J = 1.4, 15 Hz), 6.0 (1H, dd, J = 1.5, 9.0 Hz), 5.0 (1H, s); ^{13}C NMR ($CDCl_3$) δ 162.8, 134.1 (2C), 132.2, 130.67, 129.6, 127.1, 124.9, 121.7, 47.2; IR (neat) 1689, 1625, 1413, 1317, 1260, 1154, 1053 cm^{-1}; MS *m/e* 159 ($M^+ - SO_2$), 131, 77, 55; HRMS calc for $C_{10}H_9NO$ ($M^+ - SO_2$) 159.0684, found 159.0674.

3-Methyl-1,2-benzisothiazole-1,1-dioxide.

To a THF solution (30 mL) of saccharin (1 g, 5.45 mmol) at –78°C under a nitrogen atmosphere was added 1.4 M MeLi (8 mL, 11.2 mmol) dropwise. After 4 h at –78°C the reaction was quenched by adding water. The reaction was warmed to room temperature, diluted with ethyl acetate, and washed with a brine solution (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. This provided a reddish solid which was suspended in ethyl acetate and filtered to provide 518 mg (52% yield) of the sulfonyl imine, mp 207-209°C. ^1H NMR ($CDCl_3$) δ 7.94- 7.91 (2H, m), 7.8- 7.7 (3H, m), 4.8 (1H, s), 2.7 (3H, s); ^{13}C NMR ($CDCl_3$) δ 173.2, 139.5, 134.0, 133.6, 131.5, 124.1, 122.3, 17.6; IR (neat) 2930, 2361, 2345, 1545, 1317, 1171, 771 cm^{-1}; MS *m/e* 181 (M^+), 133, 117, 102, 90, 76, 50; HRMS calc for $C_8H_7NO_2S$ 181.0196, found 181.0230.

3,3-Dimethyl-1,2-benzisothiazole-1,1-dioxide.

A THF solution (3 mL) of the above sulfonyl imine (100 mg, 0.55 mmol) was cooled to –78°C under a nitrogen atmosphere. A 1.4 M MeLi solution (0.39 mL, 0.55 mmol) was added dropwise and the reaction stirred for 2 h, then warmed to room temperature. Water was added to the reaction followed by aqueous washings with 1 N HCL (10 mL) and bicarbonate solution (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 3:1) provided 28 mg of the sultam (31% yield, based on recovered starting material). ^1H NMR ($CDCl_3$) δ 7.7 (1H, d, J = 7.7 Hz), 7.6 (1H, t, J = 7.6 Hz), 7.5 (1H, t, J = 7.4 Hz), 7.4 (1H, d, J = 7.7 Hz), 4.8 (1H, s), 1.6 (6H, s); ^{13}C NMR ($CDCl_3$) δ 145.9, 134.8, 133.2, 128.9, 122.7, 120.8, 60.8, 29.4 (2C); IR (neat) 3245, 1379, 1298, 1175, 756, 725 cm^{-1};

MS *m/e* 195 (M^+), 182, 134, 117, 91, 73; HRMS calc for $C_8H_8NO_2S$ ($M^+ - CH_3$) 182.0224, found 182.0262.

3,3-Dimethyl-2-(1-oxo-2-propenyl)-1,2-benzisothiazole-1,1-dioxide, 8b.

To a mixture of sodium hydride (6 mg of a 60% dispersion, 0.15 mmol) in THF (1mL) under a nitrogen atmosphere was added a THF solution (1 mL) of the above sulfonyl imine (27 mg, 0.14 mmol). The mixture was stirred for 1 h at room temperature and then a THF solution (1 mL) of 3-chloropropionylchloride (19 mg, 0.15 mmol) was added. The mixture was stirred for 1.5 h then excess triethylamine was added. After 1.5 h, the mixture was washed with 1 N HCl, bicarbonate solution, and brine (3 x 10 mL each). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 33 mg of crude product. The ^1H NMR spectrum of the crude product showed ~30% conversion to product with ~70% remaining starting material. Flash chromatography (hexanes/ethyl acetate, 5:1) afforded 10 mg (29% yield) of **8b.** ^1H NMR ($CDCl_3$) δ 7.8 (1H, d, J = 7.9 Hz), 7.7 (1H, t, J = 7.6 Hz), 7.6 (1H, t, 7.7 Hz), 7.5 (1H, d, J = 7.7 Hz), 7.2, (1 H, dd, J = 10.4, 16.4 Hz), 6.6 (1H, dd, J = 1.4, 16.4 Hz), 5.9 (1H, dd, J = 1.5, 10.4 Hz), 1.91 (6H, s); ^{13}C NMR ($CDCl_3$) δ 163.1, 142.6, 134.5, 131.4, 131.1, 129.6, 128.5, 122.9, 121.5, 66.5, 27.3 (2C); IR (neat) 2978, 1690, 1312, 1237; MS *m/e* 251 (M^+), 236; HRMS calc for $C_{12}H_{13}NO_3S$ 251.0616 found 251.0615.

3-Phenyl-1,2-benzisothiazole-1,1-dioxide.

To a THF solution (50 mL) of saccharin (3 g, 16.4 mmol) at –78°C under a nitrogen atmosphere was added 2.0 M PhLi (16.8 mL, 33.7 mmol) dropwise. After 3.6 h water was added and the reaction mixture warmed to room temperature. The mixture was washed with a brine solution (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a solid. The solid was washed with ethyl acetate, filtered and dried to afford 2.1 g (55% yield) of the sulfonyl imine, mp 156-158°C. ^1H NMR ($CDCl_3$) δ 8.0-7.9 (3H,m), 7.9 (1H, d, J = 7.4 Hz), 7.8-7.65 (3H, m), 7.63-7.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 171.0, 140.6, 133.7, 133.3 (2C), 130.2, 130.1, 129.3 (2C), 129.1 (2C), 126.6, 122.8; IR (neat) 2357, 1532, 1304, 1169 cm^{-1} ; MS *m/e* 243 (M^+), 195, 179, 152, 76; HRMS calc for $C_{13}H_9NO_2S$ 243.0354, found 243.0368.

3,3-Diphenyl-1,2-benzisothiazole-1,1-dioxide.

To a THF solution (30 mL) of the above sulfonyl imine (1 g, 4.1 mmol) at –78°C under a nitrogen atmosphere was added 2.0 M PhLi (4.1 mL, 8.2 mmol) dropwise. The mixture was maintained at –78°C for 7.25 h then quenched by adding water. The mixture was warmed to room temperature and washed with a brine solution (3x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to provide a white solid. The solid was washed with ether and filtered to provide 1.1 g (83% yield) of the sultam, mp 203-204°C. ^1H NMR ($CDCl_3$) δ 7.8 (1H, d, J = 7.1 Hz), 7.65-7.54 (2H, m), 7.44 (1H, d, J = 7.7 Hz), 7.4-7.3 (10 H, m), 5.0 (1H, s); ^{13}C NMR ($CDCl_3$) δ 142.9, 142.8, 134.9, 133.2, 129.5, 128.6 (4C), 128.3 (2 C), 127.6 (4C), 126.6 (2C), 121.3, 72.3; IR (neat) 3343, 3273, 2361, 1451, 1285, 1157, 755, 699 cm^{-1}; MS *m/e* 321 (M^+), 256, 244, 180, 152, 102, 77, 51; HRMS calc for $C_{19}H_{15}NO_2S$ 321.0824, found 321.0812.

3,3-Diphenyl-2-(1-oxo-2-propenyl)-1,2-benzisothiazole-1,1-dioxide, 8c.

To a suspension of sodium hydride (37 mg of a 60% dispersion, 0.93 mmol) in THF (5 mL) at room temperature under a nitrogen atmosphere was added a THF solution (5 mL) of the above sultam (129 mg, 1.01 mmol). After 1.5 h a THF solution (5 mL) of 3-chloropropionylchloride was added. After stirring 11 h, excess triethylamine was added. The mixture was stirred an additional 1 h then washed with 1 N HCl (2x 20 mL) and saturated bicarbonate (2x 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Flash

chromatography (hexanes/ethyl acetate, 7:1) provided 128 mg (72% yield based on unreacted starting material) of **8c**, mp 195-197°C. ^{1}H NMR ($CDCl_3$) δ 7.84 (1H, m), 7.56-7.48 (6H,m), 7.39-7.31 (6H,m), 7.3 (1H, m), 7.2 (1H, dd, J = 6.3, 14.4 Hz), 6.4 (1H, dd, J = 1.4, 16.4 Hz), 5.9 (1H, dd, J = 1.4, 10.4 Hz); ^{13}C NMR ($CDCl_3$) δ 161.3, 141.4, 139.1 (2C), 134.5 (2C), 132.0, 131.0, 129.7, 128.5 (4C), 128.1 (4C), 128.0 (2C), 126.1, 121.0, 75.9; IR (neat) 1695, 1407, 1320, 1235, 1131, 741, 634 cm^{-1}; MS *m/e* 375 (M^+), 348, 320, 311, 283, 256, 244, 218, 165, 152, 77, 55; HRMS calc for $C_{19}H_{14}NO_2S$ ($M^+ - C_3H_3O$) 320.0745, found 320.0726.

Acrylic 2,2,5,5-tetramethyl-1,3-oxazolidinide, 10.

In a flame-dried 50mL round bottom flask, 1 g (7.8 mmoles, 1 equiv) of 2,2,5,5-tetramethyl-1,3-oxazolidine[15], 1.03 mL (9.37 mmoles, 1.20 equiv) of N-methyl morpholine and 10 mL of benzene were stirred and cooled in an ice bath. Over a five minutes, 660 μL (8.12 mmoles, 1.04 equiv) of acryloyl chloride was added. The mixture was stirred for thirty minutes at 0°C and 2 hours at room temperature. The mixture was brought up in 100 mL of ether and washed with 50 mL 10% $NaHCO_3$, 50 mL water and 75 mL of brine. The solution was dried with $MgSO_4$, filtered, concentrated and chromatographed on silica with 33% ethyl acetate in hexanes to give 982 mg (5.37 mmoles, 69% yield) of a pale yellow liquid. ^{1}H NMR ($CDCl_3$) δ 6.4 (2H, m), 5.6 (1H, d), 3.7 (2H, m), 1,7 (6H, s), 1.5 (6H, s). ^{13}C NMR ($CDCl_3$) δ 163, 130, 127, 98, 78, 59, 27, 25. IR ($CDCl_3$) 1655 cm^{-1}. GCMS (CI, CH_4/NH_3) *m/e* 201 ($M + NH_4^+$) 184 (MH^+). HRMS calc for $C_9H_{14}NO_2$ ($M^+ - CH_3$) 168.1024, found 168.1029.

Methyl, 2-iodo-3-cyclohexylpropionate.

All flasks were flame dried and the reaction was carried out under an atmosphere of argon. Freshly distilled N,N-diisopropylamine, 2.10 mL (15.0 mmole), was combined with 15 mL of dry THF. The mixture was cooled to -78°C and 6.25 mL of n-butyl lithium (2.4 M solution in hexanes) was added slowly. The mixture was stirred for 15 min then a solution of 2.50 mL (13.8 mmoles) methyl, 3-cyclohexylpropionate in 10 mL dry THF was added dropwise upon which the solution turned yellow. The mixture was stirred for 45 min then added via canula to a solution of 8.0 g (32 mmole) iodine in 30 mL dry THF at -78°C. After stirring at -78°C for 1 h the reaction mixture was removed from the cooling bath and quenched with 25 mL of saturated NaCl solution. The mixture was diluted with 150 mL of ether and washed with 3 x 20 mL of 30% $Na_2S_2O_3$ solution, 20 mL of H_2O and 20 mL of saturated brine solution. The organic layer was dried over anhydrous $MgSO_4$ and the ether was removed in vacuo to give a dark brown oil. The oil was purified by flash column chromatography (silica, 10% ethyl acetate:90%hexanes; Rf=0.56) to give 1.5 g of light yellow oil corresponding to a yield of 36%: ^{1}H NMR ($CDCl_3$) δ 4.42 (1H, t), 3.75 (3H, s), 1.9 (2H, m), 1.67 (5H, m), 0.8-1.4 (6H, m); GCMS (CI, CH_4/NH_3) *m/e* 314 ($M+NH_4^+$), 297 (MH^+). HRMS calc for $C_{10}H_{16}O_2I$ $(M-H)^+$ 295.0196, found 295.0197.

2-Iodo-3-cyclohexylpropionyl chloride.

A flame dried flask was charged with 25.0 mL (0.144 moles) cyclohexanepropionic acid (Aldrich, 99%), 70 mL (0.96 moles) thionyl chloride and 22.1 g (0.174 moles) of iodine. A $CaCl_2$ drying tube was affixed and the mixture was refluxed for 4 h then concentrated in vacuo. The residue was dissolved in approximately 30 mL of CCl_4 and cooled in an ice bath. The resulting iodine crystals were removed by filtration. After 3 succesive crystallizations, the residue was dissolved in 150 mL of CCl_4 and washed thoroughly (7-10 times) with 20 mL portions of saturated $Na_2S_2O_3$ solution to remove the remaining iodine.

The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. Vacuum distillation (bp=66°C/2 torr mm Hg) afforded 27.1 g of purple oil containing 89% iodoacid chloride (58% yield) and 11% cyclohexanepropionyl chloride by NMR. ^1H NMR ($CDCl_3$) δ 4.7 (1H, t), 2.9 [0.22H, t (acid chloride sans iodide)], 1.95 (m), 1.7 (m), 0.9-1.4 (m); IR ($CHCl_3$) 3022.4 (s), 2827.8 (s), 1778.3 (s), 1521.6 (w), 1447.9 (m), 1216.7 (s), 1038 (w), 980.5 (w), 925.0 (w) cm^{-1}.

2-Iodo-3-cyclohexylpropionic 5(S)-isopropyl-2,2-dimethyl-1,3-oxazolidinide.

A flame dried flask was charged with 2.37 g (7.89 mmoles) of 2-iodo-3-cyclohexanepropionyl chloride and 20 mL dry CH_2Cl_2. The flask was purged with argon and cooled to -78°C. A solution of 1.7 mL (12 mmoles) triethyl- amine in 4 mL dry CH_2Cl_2 was added dropwise. The solution was stirred for 15 min then a solution of 1.10 g (7.73 mmoles) 4(S)-isopropyl-2,2-dimethyl-1,3-oxazolidine in 10 mL dry CH_2Cl_2 was added slowly. The reaction mixture was stirred at -78°C for 4 h. The CH_2Cl_2 was removed in vacuo and the resulting residue was dissolved in ether then washed with 20 mL of d H_2O, 20 mL saturated $NaHCO_3$ and 20 mL saturated brine solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to afford 2.87 g of brown oil (91%). GC (100°C for 1 min, 15°C/min to 280°C) indicated the presence of two isomers with retention times of 10.3 min (75%) and 10.5 min (16%): ^1H NMR ($CDCl_3$) δ 4.41 (m), 3.95 (s), 3.85 (m), 3.55 (m), 1.8-2.1 (m), 1.7 (s), 1.5 (s), 1.2 (m), 0.95 (d of d); GCMS (CI, CH_4/NH_3) identical for both isomers *m/e* , 425 ($M+NH_4^+$), 408 (MH^+). HRMS calc for $C_{17}H_{30}NO_2I$ (M^+) 407.1321, found 407.1314 (1st diastereomer), 407.1322 (2nd diastereomer).

4-(3-Cyclohexyl-2-iodo-1-oxopropyl)(7R)-10,10-dimethyl-5-thia-4-azatricyclo [5.2.1.0] decane-5,5-dioxide.

To a THF solution (5 mL) of $NaN(TMS)_2$ (0.69 mL of 1.0 M solution, 0.69 mmol) at –78°C under a nitrogen atmosphere was added a THF solution (5 mL) of the sultam (250 mg, 0.71 mmol). After stirring at –78°C for 1 h the solution was transferred via canula into a THF solution (5 mL) of iodine (270 mg, 1.06 mmol) and HMPA (500 mg, 2.84 mmol) at –78°C. The solution was maintained at –78°C for 1 h then warmed to room temperature. The reaction mixture was washed with 1 N HCl, saturated bicarbonate solution, and saturated $NaHSO_3$ solution (2x 20 mL each). The organic layer was dried over $MgSO_4$, filtered, and concentrated. ^1H NMR of the crude reaction mixture showed a 3.6: 1 ratio of diastereomers. Flash chromatography (hexanes/ ethyl acetate, 15:1,) afforded 66 mg of iodide, 180 mg of a mixture of the two diastereomers, and 18 mg of the minor diastereomer (overall yield 79 %). Major isomer: ^1H NMR ($CDCl_3$) δ 5.08 (1H, t, J = 7.4 Hz), 3.97 (1H, dd, J = 2.0, 6.3 Hz), 3.47 (2H, dd, J = 9.8, 19.5 Hz), 2.07-1.89 (8H, m), 1.79-1.60 (4H,m), 1.42-1.22 (4H, m), 1.20 (3H, s), 1.18-1.04 (2H, m), 0.97 (3H, s), 0.95-0.82 (2H, m); ^{13}C NMR ($CDCl_3$) δ 170.2, 64.8, 53.0, 48.7, 47.8, 44.3, 42.8, 37.7, 37.0, 32.8, 32.7 (2C), 26.5, 26.3, 26.0 (2C), 20.5 (2C), 19.9; IR (neat) 2923, 2852, 1693, 1331, 1135 cm^{-1}; MS *m/e* 479 (M^+), 464, 383, 352, 270, 135; HRMS calc for $C_{19}H_{30}NO_3S$ (M^+ – I) 352.1946 found, 352.1966. Minor isomer: ^1H NMR ($CDCl_3$) δ 4.99 (1H,dd, J = 2.2, 7.7 Hz), 3.87 (1H, t, J = 6.4 Hz), 3.49 (2H, s), 2.16-2.04 (3H, m), 1.95-1.80 (6H, m), 1.74-1.54 (4H, m), 1.47-1.33 (2H, m), 1.30-1.14 (3H, m), 1.13 (3H, s), 0.97 (3H, s), 0.96-0.84 (2H, m); ^{13}C NMR ($CDCl_3$) δ 169.4, 65.8, 52.6, 48.6, 47.8, 45.5, 44.6, 38.4, 38.0, 32.9, 32.8, 32.1, 26.3, 26.2, 26.1, 26.0, 20.6; IR (neat) 2997, 2921, 2853, 1678, 1229 cm^{-1}; MS *m/e* 352 (M+ – I), 270, 257, 135, 121, 109, 93; HRMS calc for $C_{19}H_{30}NO_3S$ (M^+ – I) 352.1946 found, 352.1904.

Telomerization Procedure.

The procedure for the telomerization of 2-iodo-3-cyclohexanepropionic 5(S)-isopropyl-2,2-dimethyl-1,3-oxazolidinide with acrylic 5(R)-isopropyl-2,2-dimethyl-1,3-oxazolidinide is typical. A flame dried flask was charged with: 0.285 g (6.4 x 10^{-4} moles) 2-iodo-3-cyclohexanepropionic-5(S)-isopropyl-2,2-dimethyl-1,3-oxazolidinide, 2.5 mL (2.1 mmoles) of a 0.84 M solution of acrylic 5(R)-isopropyl-2,2-dimethyl-1,3-oxazolidinide in benzene, 3.0 mL (9.5 mmole) allyl tributylstannane and 9.0 mL dry benzene. The solution was degassed by bubbling argon through for 15 minutes. Freshly recrystallized AIBN, 10 mg, was added and the mixture was refluxed for 2 h under argon. Another portion of AIBN, 10 mg, was added and the mixture was refluxed for an additional 2 h. The benzene was removed in vacuo and the crude telomer mixture was dissolved in hexanes. A portion of remaining tin compounds were removed by passing the mixture through a short silica column with hexanes followed by ethyl acetate. The ethyl acetate extracts were combined, concentrated, diluted with ether then stirred overnight with a 10% aqueous KF solution. Derivatization and analysis of the telomer products was performed as described in the text and accompanying references.[7]

Analysis of telomerizations of **7** was performed on the product mixtures directly by GC (15m SPB-1 column, 100°C/1 min, 15°C/min ramp, final hold at 280°C/10 min.) Threo and erythro assigments were confirmed by hydrolysis of the telomers with LiOOH[16] and conversion to known methyl esters.[7]

Synthesis and Characterization of major bis-Sultam Adducts (Table 1, entry 7).

A benzene solution (12 mL) of cyclohexyliodide (388 mg, 1.8 mmol), the acryloyl sultam (930 mg, 3.45 mmol), allyl tributylstannane (2.12 g, 6.4 mmol), and AIBN (43 mg, 0.26 mmol) was heated at 80°C for 7 h under a nitrogen atmosphere. The mixture was concentrated then partitioned between hexanes/acetonitrile to remove tin byproducts. The acetonitrile layer was concentrated and the crude products purified by flash chromatography (hexanes/ethyl acetate, 15:1) affording1/1/1 adduct (416 mg, 59%), 1/2/1 *R,R*-adduct (217 mg, 18% yield), 1/2/1 *R,S*-adduct (183 mg, 15% yield), and higher telomers (414 mg). *R,R*-adduct (less polar): ^{1}H NMR ($CDCl_3$) δ 5.71 (1H, m), 5.12-4.98 (2H, m), 3.87-3.78 (2H, m), 3.54-3.36 (4H, m), 3.24-3.09 (2H, m), 2.50 (1H, m), 2.31-2.12 (3H, m), 2.06-1.80 (10H, m), 1.79- 1.50 (6H, m), 1.42-1.33 (5H, m), 1.26 (3H, s), 1.23 (3H, s), 1.22-1.00 (4H, m), 0.96 (6H, s), 0.87-0.64 (2H, m); ^{13}C NMR ($CDCl_3$) δ 174.9, 173.9, 135.2, 117.3, 65.3, 65.3, 53.1, 48.2, 47.7, 44.6, 44.5, 42.3, 40.5, 38.2, 37.3, 35.3, 35.0, 34.4, 33.3, 33.1, 32.7, 29.1, 26.5, 26.2, 20.8, 19.9; IR (neat) 2957, 2922, 2853, 2341, 2329, 1696, 1331, 1134 cm^{-1}; MS *m/e* 662 (M^+), 599, 448, 420, 351, 135, 107, 93. *R,S*-adduct (more polar): ^{1}H NMR ($CDCl_3$) δ 5.68 (1H, m), 5.16-4.98 (2H, m), 3.92-3.84 (2H, m), 3.51-3.38 (4H, m), 3.19 (1H, m), 3.03 (1H, m), 2.63 (1H, m), 2.47-2.25 (2H, m), 2.09-1.96 (4H, m), 1.91-1.73 (8H, m), 1.70-1.56 (6H, m), 1.47-1.25 (8H, m), 1.20 (3H, s), 1.12 (3H, s), 0.97 (3H, s), 0.96 (3H, s), 0.94-0.81 (2H, m); ^{13}C NMR ($CDCl_3$) δ 175.1, 174.2, 134.2, 117.5, 65.4, 65.2, 53.1, 53.0, 48.1, 47.6, 47.5, 44.6, 42.1, 39.4, 38.3, 35.2, 34.6, 33.0, 32.8, 32.3, 29.6, 26.4, 26.3, 26.0, 21.0, 19.8; IR (neat) 2958, 2922, 2853, 2361, 2335, 1685, 1331, 1213, 1116, 1039; MS *m/e* 662 (M^+), 599, 502, 448, 420, 351, 135, 107, 93.

***Erythro* and *threo* 2-(Cyclohexylmethyl)-4-(2-propenyl)-1,5-pentanediol (reference samples for Method B).**

These were prepared by standard LAH reduction of the corresponding erythro and threo dimethyl esters. Threo: ^{1}H NMR ($CDCl_3$) δ 5.81 (1H, m), 5.07-5.00 (2H, m), 3.58-3.41 (4H, m), 2.38 (2H, s), 2.07 (2H, t, J = 6.7 Hz), 1.78-1.66 (6H, m), 1.40-1.03 (9H, m), 0.90-0.83 (2H, m); ^{13}C NMR ($CDCl_3$) 136.91,

116.34, 66.13, 65.88, 39.64, 37.43, 36.44, 34.94, 34.49, 33.88, 33.53, 33.35, 26.61, 26.31(2C); IR (neat) 3326, 2922, 2851, 2360, 2330, 1447, 1034, 911 cm^{-1}. Erythro: ^1H NMR ($CDCl_3$) δ 5.78 (1H, m), 5.07-5.00 (2H, m), 3.62 (2H, dd, *J* = 4.3, 10.7 Hz), 3.46-3.36 (2H, m), 3.24-2.80 (2H, broad s), 2.07 (2H, t, *J* = 6.6 Hz), 1.71-1.58 (7H, m), 1.50 (1H, m), 1.35-1.06 (7H, m), 0.92-0.80 (2H, m); ^{13}C NMR ($CDCl_3$) δ 136.8, 116.3, 65.6, 65.1, 40.2, 37.9, 36.6, 34.828 34.7, 33.8, 33.6, 33.0, 26.6, 26.3 (2C); IR (neat) 3326, 2922, 2851, 1448, 1033, 911 cm^{-1}.

Analysis by Method B.

The crude mixture of sultam-derived addition products was freed of tin by-products by hexanes/acetonitrile extraction. No addition products were detected in the hexanes layer. The acetonitrile layer was concentrated and reduced as above with $LiAlH_4$. The entire reduced mixture was acetylated (Ac_2O/pyridine). Flash chromatography (20/1 hexanes: ethyl acetate) of the acetylated mixture gave the syn and anti diacetates as a mixture. Because of signal overlapping in the ^{19}F NMR, it was not possible to conduct the Mosher analysis on the syn/anti diol mixture. HPLC (Waters μ-poracil 7.8X 300 mm column, 20/1 hexanes: ethyl acetate, 4 mL/min.) of the diacetate mixture provided pure syn and anti diastereomers, with the anti diacetate eluting first. Diastereomer ratios determined by intergration of the HPLC trace were identical with isolated yields, and comparable with the diastereomer ratios determined at the stage of the sultam adducts (by separation and isolation) or the diols (by GC). The individual diacetates were each reduced with $LiAlH_4$ to provide pure syn and anti diols. These diols were then derivatized with Mosher's acid chloride as described below.

Preparation of Mosher's ester derivatives.

To a methylene chloride solution (1 mL) of the diol (5 mg, 0.021 mmol), triethylamine (14.6 μL, 0.1 mmol), and DMAP (catalytic) was added Mosher's acid chloride (14.6 uL, 0.052 mmol). After 16 h at 25C, the mixture was washed with 1N HCl and saturated bicarbonate solution. The organic layer was dried over $MgSO_4$, filtered and concentrated. ^1H NMR and TLC analysis indicated complete consumption of starting material: ^{19}F NMR ($CDCl_3$, $CFCl_3$ as internal standard), from racemic anti (*R,R/S,S*-5) diol: δ -71.84 and -71.91, -71.95, -71.96; from racemic syn (*R,S/S,R*-5) diol: δ -71.89, -71.95 (ratio of peaks, 3:1). Reaction of an anti-diol sample enriched in *R,R*-5 with (*S*)-Mosher's acid attributed the downfield pair of resonances to the derived diester. Reaction of a syn-diol sample enriched in *R,S*-5 with (*S*)-Mosher's ester showed two very closely spaced resonances at -71.88 and -71.89. These overlapped a resonance derived from the diester of *S,R*-5, and a correction was made by subtration of an amount equal to the area of the other resonance of this diastereomer at -71.95.

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