A New Chiral Auxiliary for Asymmetric Thermal Reactions: High Stereocontrol in Radical Addition, Allylation, and Annulation Reactions

Jeffrey G. Stack, Dennis P. Curran,*[1] Steven V. Geib,[2] Julius Rebek, Jr.,*[3a] and Pablo Ballester[3b]

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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Abstract: A new imide chiral auxiliary, *endo*-7-(2-benzoxazolyl)-1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one (**5**), is prepared from Kemp's triacid and resolved via its menthyl carbamate. Mixed fumarate derivatives of the auxiliary show unprecedented control of regiochemistry and β-stereochemistry in representative radical addition reactions. Chiral radicals derived from **5** also show extremely high levels of stereoselectivity in representative radical allylation and cyclization reactions, Structural features of the chiral auxiliary and features of radical addition are integrated into a model for stereoselection.

The development of new auxiliaries for the control of stereochemistry in carbon–carbon bond formation has received considerable attention,[4] We have reported the use of new auxiliaries derived from Kemp's triacid[5] in enolate alkylations[6] and in thermal, non-Lewis acid catalyzed reactions such as nitrile oxide cycloadditions,[7] We have recently developed a versatile Kemp's triacid auxiliary that has shown excellent stereocontrolling properties in radical addition reactions,[8] We now describe in detail the synthesis, structural characterization, and asymmetric radical reactions promoted by this auxiliary, When attached to an alkene, this auxiliary provides the first example of high regio- and β-stereocontrol in radical additions to mixed fumarimides, When attached to a radical, the auxiliary provides record levels of induction in asymmetric allylation and annulation reactions.

Synthesis of Auxiliary 5. Scheme I outlines the assembly of the auxiliary **5**, which begins with 1,3,5-trimethyl-1,3,5-cyclohexanetricarboxylic acid (**3**; Kemp's triacid), The triacid is commercially available, but for this work it was prepared from 1,3,5-cyclohexanetricarboxylic acid (**1**)[9] by a small modification of the published procedures.[10] The racemic auxiliary *rac*-**5** is prepared in six steps and 62% overall yield from Kemp's triacid with no purification of the intermediates necessary, The synthesis is straightforward and brief enough to allow the preparation of 1–2 g of auxiliary. The route to the auxiliary begins by selective manipulation of the carboxylic acid functions, Cyclic imide formation occurred in 91% yield simply by heating the triacid **3** and urea in triglyme at 200 °C.[5c] An acid chloride, formed by heating the imide acid with excess $SOCl_2$ at 80 °C, was treated with 2-aminophenol to give the imide amide **4** in 92% yield. Stepwise reduction of one carbonyl of the imide—first with $NaBH_4$ in methanol at 0 °C, and then with triethylsilane in trifluoroacetic acid—provided a lactam amide (84%) in which the last vestiges of the symmetry in Kemp's triacid had disappeared, Heating this compound with $SOCl_2$ and pyridine in benzene at 90 °C afforded the racemic auxiliary **5** in 89% yield.

Resolution of the racemic auxiliary was accomplished by derivatization of the lactam with a chiral reagent and separation of the diastereomeric mixture, Several reagents were examined, and (−)-menthyl chloroformate was found to give readily separable diastereomers, Deprotonation of the lactam with *n*-BuLi in THF at −78 °C and acylation of the anion with (−)-menthyl chloroformate afforded the chiral carbamate **6** as a mixture of diastereomers, Separation of the diastereomers was easily effected by flash chromatography, and the optically active auxiliaries were regenerated by treatment of (*R*)- or (*S*)-**6** with trifluoroacetic acid (40% and 36% yields overall from *rac*-**5**).

The absolute configuration of the auxiliary was determined by a single-crystal X-ray structure of the more polar menthyl diastereomer, (*R*)-**6**, The structure (Figure 1a) is unusual in one aspect—the carbonyl groups are not opposed as is usually found in acyclic imide linkages, The near alignment of the carbonyl dipoles is caused by configurational "mismatching" of the two parts of (*R*)-**6**, If all acyclic bonds are placed in their favored rotational orientations, then the benzoxazole ring and the isopropyl of the menthyl ring group literally collide. The least costly way to relieve this steric interaction is by rotating the imide N–CO bond. This partially aligns the two imide carbonyls, and this unfavorable alignment probably accounts for the large difference in polarity observed between (*R*)- and (*S*)-**6**, As expected, (*R*)-**6** is more polar, (*S*)-**6** is made of matching halves, and all bonds can exist as favored rotamers without significant problems. The global minimum of (*S*)-**6** as determined by molecular mechanics calculations is shown in Figure 1b,

Addition of Radicals to Chiral Fumarimides. Recent progress in control of acyclic stereoselection in radical reactions has provided useful levels of asymmetric induction.[11] Several groups have reported high stereoselectivities in the reactions of chiral radicals with achiral radical acceptors.[12] Additionally, Porter[13] and

(1) Dreyfus Teacher–Scholar, 1986–1991. NIH Research Career Development Awardee, 1987–1992. ICI Pharmaceuticals Awardee, 1990.

(2) Director of the University of Pittsburgh Department of Chemistry Crystallography Facility.

(3) Current addresses: (a) Department of Chemistry. The Massachusetts Institute of Technology, Cambridge, MA 02139. (b) Departamento de Quimica, Universidad de les Illes Balears, 07071 – Palma de Mallorca, Spain.

(4) (a) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 456–478. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Berlag: Berlin 1986; Vol. 4, pp 262–306. (c) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14–20. (d) Davies, S. G. *Chem. Ber.* **1989**, *122*, 268–72. (e) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241–60.

(5) (a) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1981**, *46*, 5140–43. (b) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Parris, K.; Williams, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1082–90. (c) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426–31.

(6) Jeong, K.-S.; Parris, K.; Ballester, P.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 555–56.

(7) Curran, D. P.; Jeong, K.-S.; Heffner, T. A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 9238–40.

(8) Stack, J. G.; Curran, D. P.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1991**, *113*, 5918–20.

(9) (a) Steitz, A., Jr. *J. Org. Chem.* **1968**, *33*, 2978–79. (b) Newman, M. S.; Lowrie, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 4598–4600. (c) Now commercially available from Aldrich Chemical Co.

(10) Full details for the preparation of the Kemp's triacid are contained in the supplementary material. The procedures follow published ones (ref 5c), except that toluene is used as the solvent for the key trimethylation.

(11) Porter, N. A.; Curran, D. P.; Giese, B. *Acc. Chem. Res.* **1991**, *24*, 296.

(12) (a) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738–40. (b) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740–41. (c) Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-G. *J. Am. Chem. Soc.* **1990**, *112*, 6741–42. (d) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969–80. (e) Porter, N. A.; Breyer, R.; Swann, E.; Nally, J.; Pradhan, J.; Allen, T.; McPhail, A. T. *J. Am. Chem. Soc.* **1991**, *113*, 7002–12. (f) Beckwith, A. L. J.; Hersberger, R.; White, J. M. *J. Chem. Soc., Chem. Commun.* **1991**, 1151–2. (g) Porter, N. A.; Bruhnke, J. P.; Wu, W.-X.; Rusenstein, I. J.; Breyer, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 7788–89.

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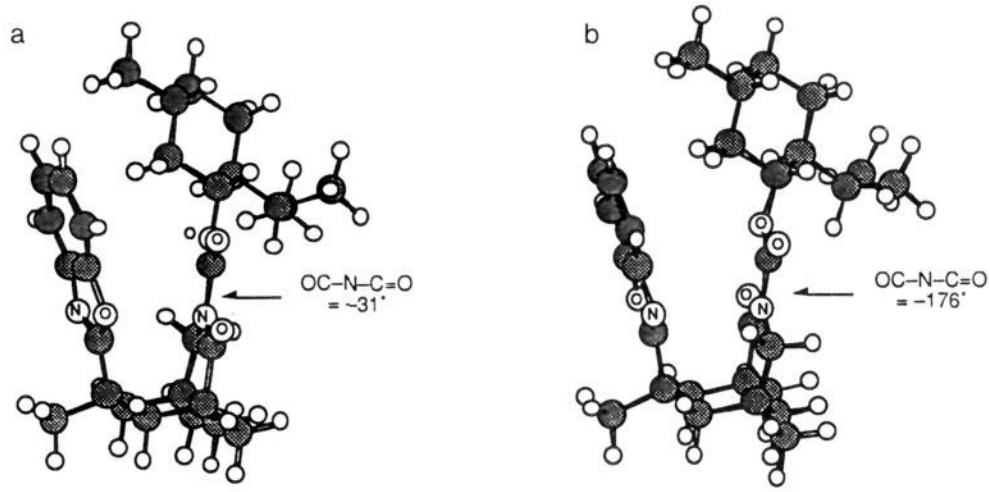
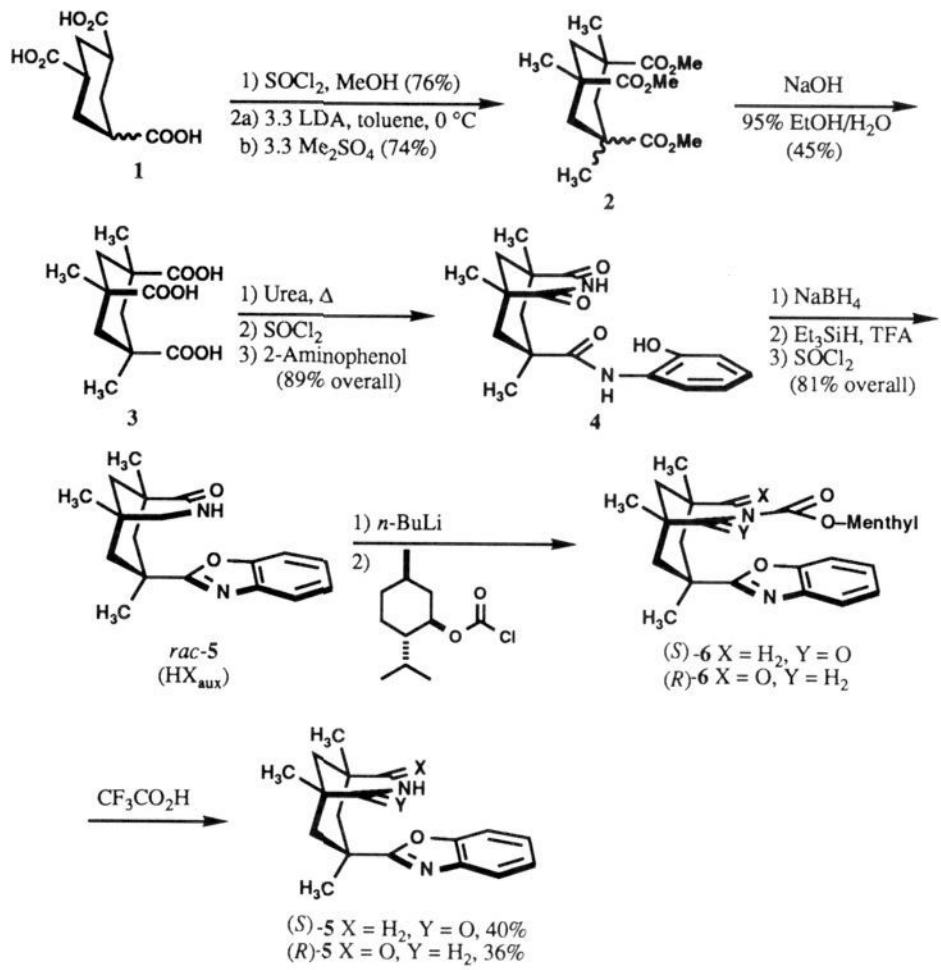
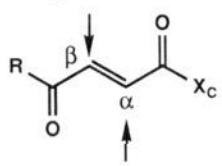


Figure 1. (a) X-ray crystal structure of (*R*)-**6**. (b) MM2 minimized structure of (*S*)-**6**.

Scheme I



Giese[13a,c] have observed high α-stereoselection in the addition of achiral radicals to amide-substituted alkenes containing the chiral controller 2,5-dimethylpyrrolidine. Despite the excellent stereoselection, Porter and Giese sometimes found it difficult to efficiently control the regiochemistry in the addition to unsymmetrical alkenes. Further, when radicals added β to the auxiliary, stereoselection was nonexistent. Our approach develops an auxiliary that can control β-stereochemistry, exploiting the propensity of nucleophilic radicals to add β to activating groups.

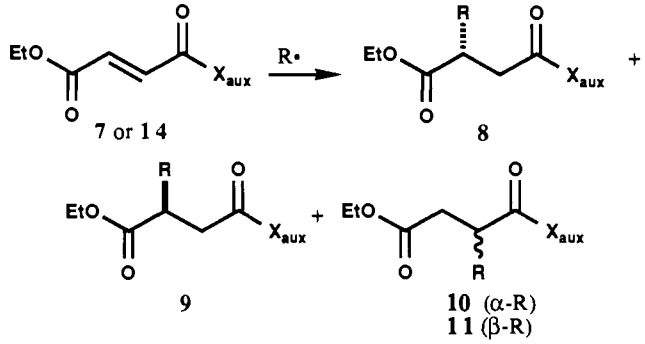


α-attack, good stereocontrol with
X_C = *trans*-2,5-dimethylpyrrolidine
β-attack, no stereocontrol

The preparation of the fumarimide substrates initially proved

(13) (a) Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc.* **1991**, *113*, 1791–99. (b) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679–82. (c) Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H. G.; Lindner, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 8311–12. (d) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309–10.

Table I. Additions to Mixed Fumarates



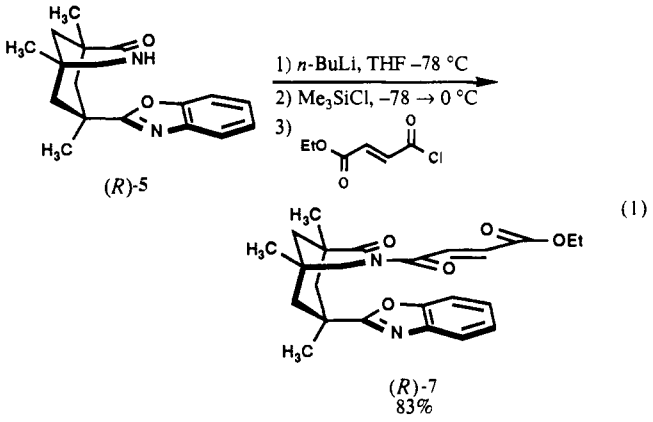
Series **8**-**10**:
a, HX_{aux} = **5**, R = *t*-butyl
b, HX_{aux} = **5**, R = cyclohexyl
c, HX_{aux} = **5**, R = *n*-hexyl
d, HX_{aux} = **13**, R = *t*-butyl

entry	substrate	R•	method[a]	temp, °C	ratio, **8**:**9**:**10**[b]	% yield
1	*rac*-**7**	*t*-Bu	tin	80	78:19:3	64
2	*rac*-**7**	*t*-Bu	mercury	25	88:9:3	*c*
3	(*S*)-**7**	*t*-Bu	mercury	0	88:9:3	69
4	*rac*-**7**	*t*-Bu	mercury	−20	96:4:*d*	*c*
5	*rac*-**7**	*t*-Bu	mercury	−40	97:3:*d*	70
6	(*R*)-**7**	cyclohexyl	mercury	−20	94:6:*e,f*	68
7	(*R*)-**7**	hexyl	mercury	0	82:18:*e,f*	42
8	**14**	*t*-Bu	mercury	0	65:35:*e,f*	75

[a] Tin: syringe pump addition of Bu_3SnH (0.66 M, 4.1 equiv) and AIBN (0.08 M, 0.5 equiv) in C_6H_6 added to **7** (0.16 M) and *tert*-butyl iodide (0.32 M, 4.0 equiv) in C_6H_6 at 80 °C for 6 h. Mercury: fumarimide **7** (0.08 M) and alkylmercuric halide (1.5 equiv) in CH_2Cl_2 stirred with excess solid $NaBH_4$ and H_2O for 2 h. [b] Ratios determined by capillary GC. [c] Not isolated. [d] Less than 2% detected. [e] Products are enantiomers of **8** and **9**. [f] Regioisomer not located.

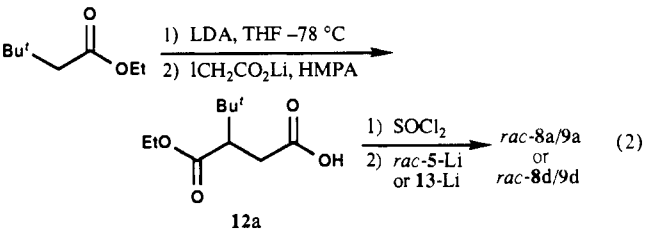
to be troublesome. Several lactam acylation procedures (MeMgBr or *n*-BuLi[14] followed by ethyl fumaryl chloride, or tertiary amine and ethyl fumaryl chloride) gave poor yields (<40%) of the desired fumarimide substrate **7**. Highly activated alkenes (acrylates, fumarates) tend to undergo destructive side reactions under these standard acylation conditions, We reasoned that a "soft" (nonbasic) yet active derivative of the lactam might minimize the tendency for byproduct formation. *N*-Silyl lactams have been used infrequently as activating agents,[15] possibly due to their moisture sensitivity, Sakakibara and Matsui[15a] have reported their successful use in the preparation of activated alkene derivatives, We developed a modified procedure that is a hybrid of the above lactam acylation technology and gives high yields of **7** (eq 1). The key to the success of this method is the in situ formation of the *N*-trimethylsilyl lactam by treatment of the auxiliary **5** with *n*-BuLi in THF at −78 °C and quenching the anion with chlorotrimethylsilane. Acylation of the *N*-silyl derivative with ethyl fumaryl chloride gives **7** in 83% yield. This acylation procedure has considerable generality,

Radical additions to **7** were performed by either the "tin method"[16] at 80 °C or by the "mercury method"[17] at ambient temperature or below. Using the tin method, syringe pump addition of a solution of Bu_3SnH (4.1 equiv) and AIBN (0,5 equiv)



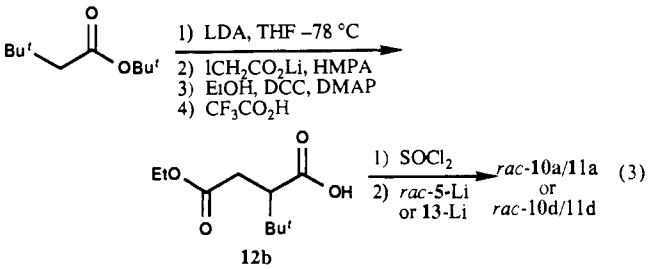
(1)

in C_6H_6 to a solution of *rac*-**7** (0.16 M) and *tert*-butyl iodide (4,0 equiv) in C_6H_6 at 80 °C over 6 h afforded a mixture of the *tert*-butyl addition products **8**, **9**, and **10** in a ratio of 78;19:3. The combined isolated yield was 64% after flash chromatography (Table I, entry 1), The product distribution was determined by VPC analysis of the crude reaction mixture and was correlated with authentic mixtures of each of the regioisomeric diastereomers, These authentic samples were prepared by acylation of the auxiliary with the racemic regioisomers of ethyl *tert*-butylsuccinic acid chloride (eqs 2 and 3). The two major products **8** and **9** are stereoisomers, The extent of asymmetric induction of the minor product **10** (a regioisomer of **8** and **9**) could not accurately be determined but is assumed to be ≥90% de based on the α-stereoselectivities in radical reactions for this auxiliary (see below), The stereochemistry of **10** is tentatively assigned based on the model described below,



(2)

12a



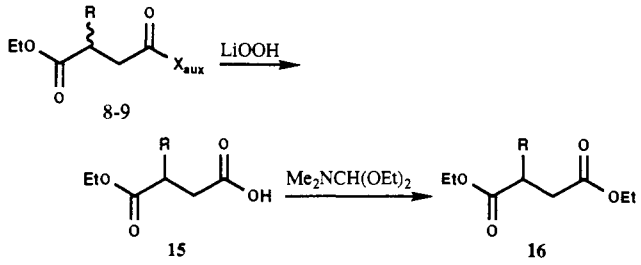
(3)

12b

The stereoselection observed above was encouraging, so we proceeded to lower the reaction temperature. We found the reduction of alkylmercuric halides, as developed by Giese,[17] to be a convenient source of alkyl radicals at low temperatures, The tin method was less convenient because chains did not propagate efficiently at low temperatures and because more extensive purification (to remove tin-containing products) was required. Higher selectivities were indeed obtained at lower temperatures, as summarized in Table I, Treatment of a CH_2Cl_2 solution of (*R*)-**7** (0.08 M) and 1,5 equiv of *tert*-butylmercuric chloride with several equivalents each of solid $NaBH_4$ and H_2O at 0 °C gave a 69% isolated yield of **8**, **9**, and **10** in a 88;9;3 ratio (entry 2). Below 0 °C, the minor regioisomer was not detected in the VPC of the crude reaction mixture, and the diastereoselectivity increased to ≥96:4 (entries 3, 4, and 5), Decreasing the steric bulk of the incoming radical had a measurable effect on the stereoselectivity of the addition: cyclohexyl (88% de, entry 6) and hexyl (64% de, entry 7) radicals afforded the β-addition products in 68% and 42% isolated yield, respectively.[18] We suspect that minor amounts

(14) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–56.
(15) (a) Sakakibara, M.; Matsui, M. *Agric. Biol. Chem.* **1973**, *37*, 1139–43. (b) Kricheldorf, H. R.; Leppert, E. *Synthesis* **1975**, 592–93. (c) Rothe, M.; Tőth, T. *Chem. Ber.* **1966**, *99*, 3820–29. (d) Yamamoto, Y.; Kimura, H. *Chem. Pham. Bull.* **1976**, *24*, 1236–41.
(16) (a) Burke, S. D.; Fobare, W. B.; Arminstead, D. M. *J. Org. Chem.* **1982**, *47*, 3348–50. (b) Giese, B.; Dupuis, J. *Angew. Chem., Int. Engl.* **1983**, *22*, 622–23. (c) Giese, B.; Gonzălez-Goměz, J. A.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 69–70.
(17) Giese, B.; Meister, J. *Chem. Ber.* **1977**, *110*, 2588–2600.

Table II. Cleavage of Radical Addition Products 8 and 9 to Succinates 15 and the Auxiliary 5

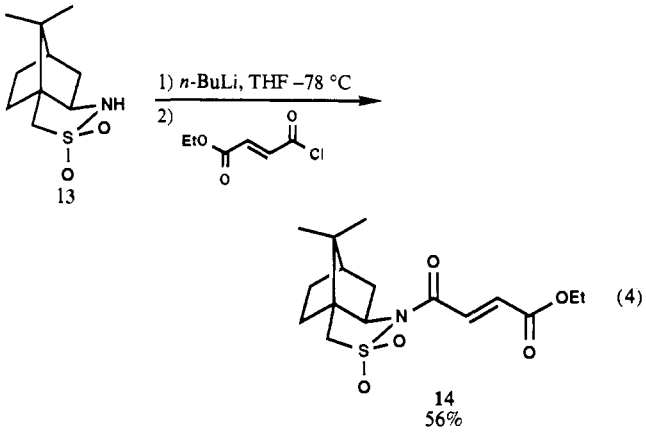


entry	R	% yield 15	$[\alpha]_D$	config	% recovery 5[b]
1	*t*-Bu	95	+14.1°	*S*	82
2	cyclohexyl	87	−10.6°[a]	*R*	83
3	hexyl	79	−7.6°[a]	*S*	89

[a] Rotation of diethyl ester 16. [b] Isolated yield after flash chromatography.

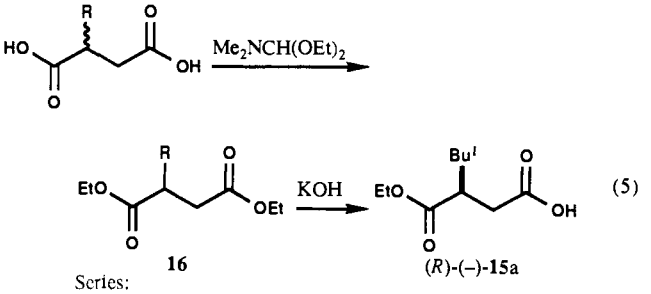
of regioisomers 10 are also present in these last two examples, and experiments to confirm this suspicion are in progress.

We also performed radical additions by using Oppolzer's camphor sultam 13 as the auxiliary, The preparation of the fumarate derivative 14 is shown in eq 4. Addition of *tert*-butyl radical at 0 °C to the fumarate derivative 14 affords mainly the β-addition products 8 and 9 in 75% yield as a 65;35 mixture of diastereomers (Table I, entry 8). No attempt was made to determine the identity of the major isomer. Thus, the benzoxazole auxillary exhibits an unprecedented combination of high regio- and β-stereoselectivity in radical additions to chiral, unsymmetrical alkenes, Other chiral auxiliaries capable of controlling α-stereochemistry (like 2,5-dimethylpyrrolidine or Oppolzer's sultam) are incapable of controlling either (or both) regio- or β-stereochemistry.



(4)

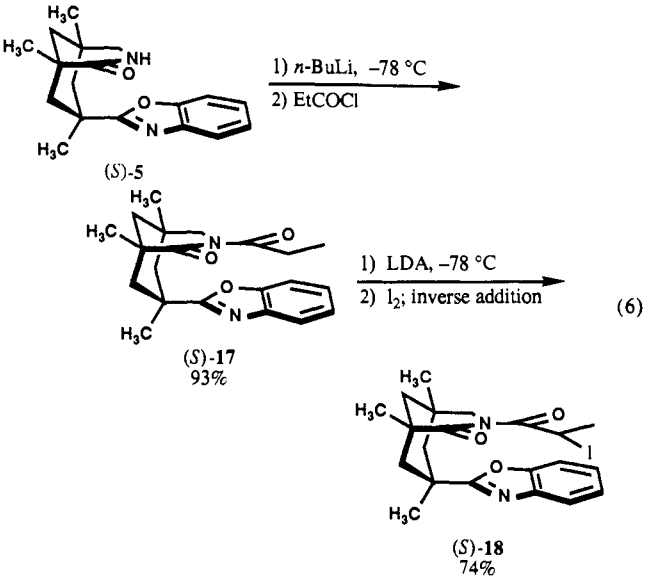
Absolute Configurations. The absolute configurations of the addition products were determined by removal of the chiral auxiliary and correlation of the succinic acid derivatives to known compounds, A dividend of this auxiliary, in addition to its excellent regio- and stereocontrolling properties, is its ease of removal and recovery after use. The imide bond to the auxiliary is readily hydrolyzed with lithium hydroperoxide[14,19] to give the carboxylic acid and the recovered benzoxazole lactam 5. As Table II shows, these conditions allow isolation of the succinic half-ester 15 and recovery of 5 in high yield. By comparing the sign of the rotation of the half-ester 15 (entry 1) or the diethyl esters 16 (entries 2 and 3) with compounds derived from optically pure alkylsuccinic acids,[20] we assigned the absolute configurations, The authentic samples of the optically pure succinic acid derivatives 16b and 16c were prepared by esterifying the diacids with *N*,*N*-dimethylformamide diethyl acetal.[21] With 16a, selective saponification of the less-hindered ester gave 15a (eq 5).



(5)

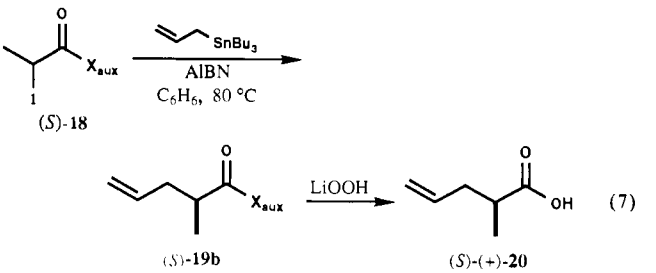
Series:
(*R*)-(−)-**16a**, R = *t*-butyl
(*S*)-(+)-**16b**, R = cyclohexyl
(*S*)-(−)-**16c**, R = *n*- hexyl

Radical Allylation and Annulation Reactions. The ability of the auxiliary to control stereochemistry at the ρ-(radical[11]) center in radical reactions was also examined by performing radical allylation and annulation reactions on appropriate substrates.[12a] For the allylation, the α-iodopropionimide substrate 18 was prepared in two steps. Acylation of the lithium salt of auxiliary (*R*)-5 with propionyl chloride proceeded in 93% yield (eq 6); the use of the *N*-silyl lactam is not necessary for acylation with saturated acid chlorides.[6] Iodination of the imide enolate (generated by treatment of the propionimide 17 with LDA at −78 °C), furnished the α-iodo derivative 18 (mainly one diastereomer, but not carefully quantitated) in 74% yield,



(6)

The allylation reaction was carried out by using the standard procedure of Keck and co-workers[22] (eq 7), Heating of a solution



(7)

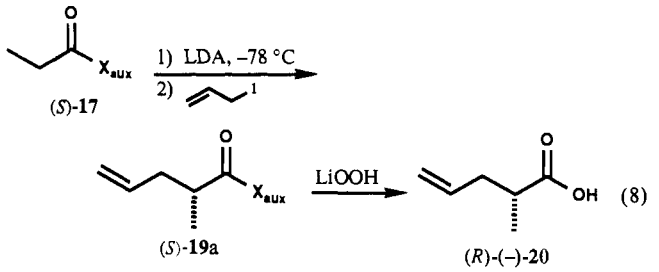
(18) Since we did not prepare authentic samples for entries 6 and 7, we cannot be completely certain that the minor isomer is a stereoisomer (not a regioisomer) of the major isomer. Only two products are detected by ^{1}H NMR and GC analyses.

(19) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–44.

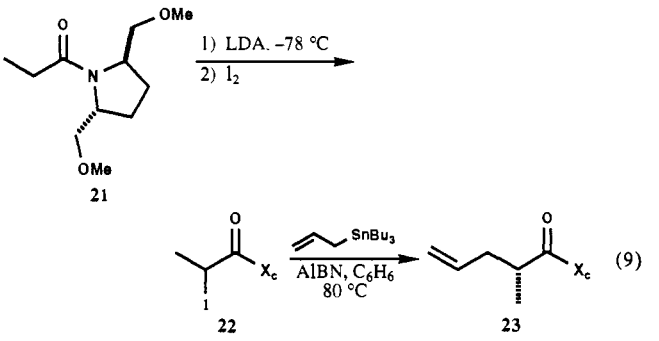
(20) (a) (*R*)-(−)-*tert*-Butylsuccinic acid, $[\alpha]^{20}_D = -26.5°$ (*c* 5, acetone): Pdoński, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 629–37. (b) (*S*)-(+)-Cyclohexylsuccinic acid, $[\alpha]^{30}_D = +26.3°$ (*c* 1.937, EtOH) Naps, M.; Johns, I. B. *J. Am. Chem. Soc.* **1940**, *62*, 2450–57. (c) (*S*)-(−)-Hexylsuccinic acid, $[\alpha]^{15.8}_D = -26.6°$ (*c* 4.00, EtOH): Wren, H.; Burns, H. *J. Chem. Soc.* **1920**, *117*, 266–68. We would like to thank N. A. Porter at Duke Univeristy for providing samples of the latter two acids.

(21) (a) Vorbrüggen, H. *Liebigs Ann. Chem.* **1974**, 821–34. (b) Brechbühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1965**, *48*, 1746–71.

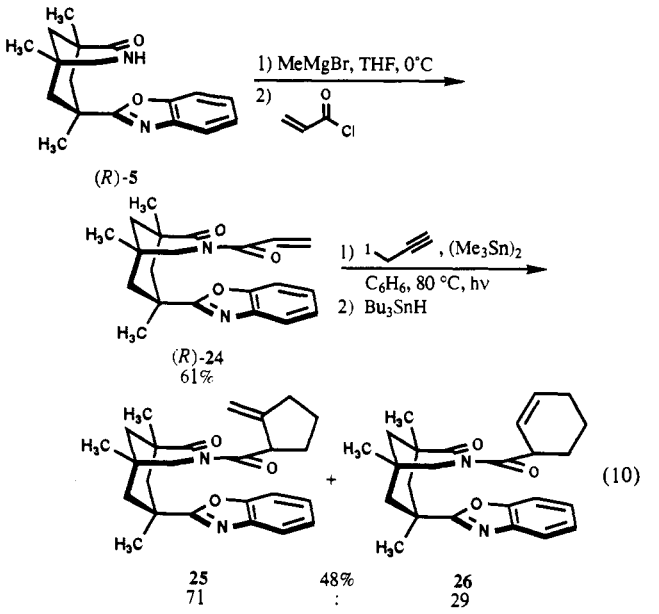
of the iodide **18** (0.35 M), allyltributylstannane (2,0 equiv), and AIBN (5 mol%) in benzene at 80 °C for 4 h afforded the allylated product (*S*)-**19a/b** in 38% yield as a 4;96 mixture of diastereomers (analysis of the crude mixture by ^{1}H NMR spectroscopy and VPC), Allylation of the lithium enolate of the propionimide (*S*)-**17** at −78 °C produced a 97,5;2.5 mixture of diastereomers (*S*)-**19a/b** in 56% yield after chromatography (eq 8), The complementary selectivity of the radical and ionic allylations allows ready quantitation of the diastereomeric mixtures, Given that the temperature of the radical reaction is 160 °C higher than the enolate alkylation, the level of selectivity is impressive, Confirmation of the stereochemistry in the two allylations is provided by comparison of the rotations of the optically active 2-methyl-4-pentenoic acids (**20**) obtained by hydrolytic cleavage of each of the allylation products. The signs of the rotations are indeed opposite, and these signs also provide the absolute configurations of the allylation products,[23]



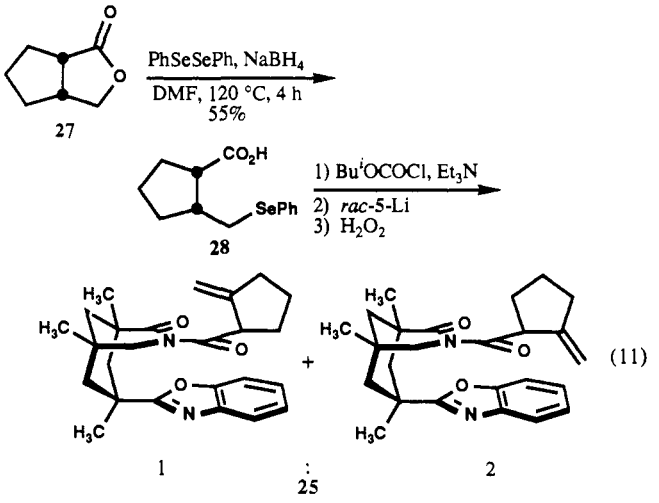
For comparison purposes, we performed a radical allylation with the α-iodopropionamide **22** derived from (2*R*,5*R*)-2,5-bis(methoxymethyl)pyrrolidine,[12b,13b] The standard Keck conditions give a 96;4 mixture of diastereomers **23a/b** in 55% yield (eq 9), In this case, the major product **23a** of the radical allylation is identical to the major diastereomer obtained by enolate allylation (>97/3 at −78 °C),[24]



The benzoxazole auxiliary is also an efficient stereocontroller in atom transfer annulation reactions,[12a,25] The requisite acrylimide **24** was prepared in 61% yield by acylation of the benzoxazole (*R*)-**5** under the conditions of Evans and co-workers (eq 10),[14] Standard atom-transfer conditions were used for the annulation;[25] a solution of acrylimide **24**, 4-iodobutyne (2–3 equiv), and hexamethylditin (two 0,1 equiv portions) in benzene (0,3 M) was heated at 80 °C and irradiated with a sunlamp for 2 h, producing a mixture of vinyl iodides, Bu_3SnH reduction of this crude mixture gave the methylenecyclopentane **25** (the product of 5-exo ring closure) and the cyclohexene **26** (the product of 6-endo ring closure) in a 71:29 ratio, The 6-endo product **26** appeared to be a single diastereomer, though we did not do a careful analysis. The 5-exo product was determined to be a 99;1 mixture of diastereomers by analysis of the ^{1}H NMR spectrum in comparison with an authentic mixture of 5-exo diastereomers. The stereochemistry of **25a** was assigned by applying the model (see below).



The synthesis of the authentic mixture was accomplished by the indirect method indicated in eq 11, Sodium phenyl selenide ring opening[26] of the lactone **27**[27] afforded the acid **28** in 55% yield. Coupling with *rac*-**5** via the mixed anhydride and oxidation of the crude seleno imide with H_2O_2 gave **25** in 10% yield as a 2;1 mixture of diastereomers after chromatography, The minor diastereomer corresponded to the major diastereomer in the radical annulation.



Discussion

To rationalize the observed high levels of both β- and ρ-stereoselection, we propose models that combine the conformational features of the benzoxazole auxiliaries with standard concepts of radical addition reactions,[11] An explanation for the observed diastereoselectivity is provided by the model presented in Figure 2b, This model is based on the MM2-minimized structure of **7** shown in Figure 2a, Good conformer control is provided by the dipole repulsion of the imide carbonyls and by the preference of the fumaroyl OC–Cαβ bond to exist s-cis, The planes of the benzoxazole and fumaroyl groups emerge from the bicyclic system too close for maximum π-stacking, and, as a result, they diverge. The benzoxazole ring extends far enough to efficiently shield the

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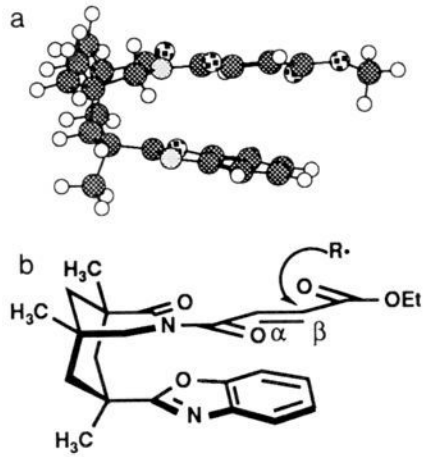

Figure 2. (a) MM2 minimized structure of **7**. (b) Transition-state model for addition.

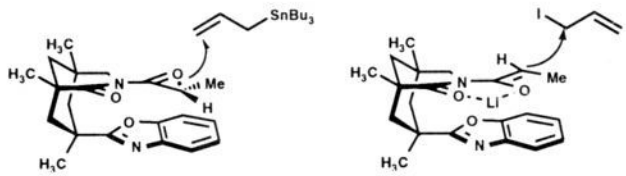

Figure 3. Transition-state models for radical and ionic allylations of benzoxazole propionimides.

face of the olefin at the β-position.

Two low-energy rotamers of the intraannular bond to the benzoxazole ring are possible, and these simply interchange the benzoxazole N and O. Both MM2 and AM1 calculations[28] suggest the rotamer with the benzoxazole C=N anti to the lactam C=O (shown in Figure 2a/b) is very close in energy to the C=N/C=O syn rotamer. The only crystal structure currently available in this series (menthyl derivative in Figure 1) shows the C=N/C=O anti rotamer.

Given the proximity of the benzoxazole ring and the fumaroyl group, we expected that there might be a significant barrier to rotation of the intraannular bond to the benzoxazole. However, the ^{1}H NMR spectra of all the compounds exhibited single sets of sharp lines. Acryloyl derivative **24** was cooled to −80 °C without any evidence for temperature dependent processes in the ^{1}H NMR spectrum.[29] Thus we do not know with certainty whether the benzoxazole intraannular bond exists primarily as one rotamer, or whether there are two rotamers present that remain in rapid equilibrium on the ^{1}H NMR time scale down to −78 °C.

The origin of the regioselectivity in the radical addition is not readily apparent. Preliminary competition experiments between various fumarimide and acrylimide derivatives and diethyl fumarate and methyl acrylate have been performed. They indicate that the regioselectivity is *not* due to increased activation of the β-position of the alkene by the carboximide with respect to the carbethoxy substituent. By implication then, the carboximide must decelerate attack in the α-position. Detailed studies on the regioselectivity effect are nearing completion and will be reported in due course.

The observed selectivities in the radical and ionic allylations can be explained by a model similar to that presented for the radical additions to the fumarimides described above. As shown in Figure 3, conformer control in the radical allylation is provided by the dipole repulsion of the imide carbonyls and the Z-geometry of the radical,[30] and the face-shielding is provided by the benzoxazole ring. Chelation in the enolate reaction causes the opposite face of the propionyl substituent to be exposed, and results in opposite selectivity.[6]

The ρ-selectivities in radical allylations and annulations with the benzoxazole imide at 80 °C equal or exceed the best current selectivities of existing auxiliaries at much lower temperatures.[12g] However, there are unfavorable features in each radical reaction. In the allylation, the isolated yield of **19** is only 38%, far lower than desirable. In the annulation, the yield is about that expected (48% observed, ~50% typical[25]), but the exo/endo selectivity is much lower than expected (71/29 observed, 90/10 typical[25]). Thus, mounting circumstantial evidence in both chiral alkene and chiral radical derivatives of **5** points to an unusual reactivity pattern in the α-position to the benzoxazole imide.

Conclusions

The new benzoxazole derivatives provide record levels of asymmetric induction in radical allylations and cyclizations (chiral radicals), and they are the first auxiliaries to control regio- and β-stereoselectivity in radical additions (chiral alkenes). Compared to existing classes of chiral auxiliaries, benzoxazole **5** is probably lacking in one key area: its synthesis is not sufficiently short. However, an improved synthesis could make **5** more readily available. New, more readily available classes of auxiliaries might be designed with the knowledge gained from **5** and its derivatives. Further, if the unusual reactivity effects in the position α to the chiral auxiliary could be fathomed, then new practical advances (for example, in regioselective additions of radicals to mixed fumarate derivatives) should result. Our current efforts are directed toward these ends.

Experimental Section

General Methods. All reactions involving air- or moisture-sensitive reagents were performed under an inert atmosphere (Ar or N_2). Benzene and THF were distilled from sodium–benzophenone; toluene, triglyme, diisopropylamine, and CH_2Cl_2 were distilled from CaH_2; pyridine was distilled from CaO; and $SOCl_2$ was distilled from limonene and linseed oil before use. All other reagents were used as received from commercial sources. Concentrations of optical rotations are expressed in units of g per 100 mL.

***endo*-*N*-(2-Hydroxyphenyl)-1,5,7-trimethyl-2,4-dioxo-3-azabicyclo-[3.3.1]nonane-7-carboxamide (4).** In a 100-mL flask was placed a stirring bar, triacid **3** (10.7 g, 41.4 mmol), and urea (3.36 g, 55.9 mmol). The flask was fitted with a condenser and flushed with Ar, and triglyme (40 mL) was added by syringe. The flask was immersed in an oil bath maintained at 200 °C for 2.5 h. The mixture was allowed to cool, and hexanes (120 mL) were added. The resulting white solid was filtered, washed with hexanes, and briefly dried in vacuo. This solid was stirred with 3 M HCl (100 mL) for 0.75 h and then placed in a 0 °C refrigerator for 12 h. The solid was collected on a fritted disc, washed with cold H_2O, and dried, first under reduced pressure and then in air for 18 h, to give a white, powdery solid (9.16 g, 92%): ^{1}H NMR δ 1.15 (d, 2, J = −13.6), 1.22 (s, 6), 1.23 (s, 3), 1.34 (d, 1 J = −15), 1.96 (d, 1, J = −15), 2.70 (d, 2, J = −15), 10.53 (br s, 1); ^{13}C NMR δ 25.10, 31.16, 40.18, 42.17, 44.22, 44.60, 177.92, 178.27; MS calcd for $C_{12}H_{17}NO_4$ 239.1158, found 239.1158.

A solution of the foregoing imide acid (2.03 g, 8.50 mmol) was heated at 85 °C in $SOCl_2$ (28 mL, 45.7 g, 380 mmol) for 2 h. The $SOCl_2$ was concentrated by simple distillation at atmospheric pressure to ~7 mL. Addition of hexanes (20 mL) resulted in the formation of a white solid. The flask was chilled to −20 °C for 1 h, and the solid was collected on a fritted disc, washed with pentane, and dried in vacuo to give a white, crystalline solid (2.04 g, 96%), mp 183–185 °C, that was used without further purification: ^{1}H NMR δ 1.29 (s, 6), 1.34 (d, 2, J = −13.9), 1.37 (s, 3), 1.42 (d, 1, J = −13.6), 2.04 (d, 1, J = −13.5), 2.77 (d, 2, J = −13.9), 7.68 (br s, 1).

A stirred solution of the above acid chloride (2.04 g, 7.92 mmol) in CH_2Cl_2 (50 mL) was treated with 2-aminophenol (1.11 g, 10.2 mmol) and pyridine (960 μL, 939 mg, 11.9 mmol). The flask was fitted with a condenser and was heated at 45 °C for 36 h. The reaction mixture was

(28) MM2 calculations were conducted on fumaroyl derivative **7** and are summarized in the supplementary material. AM1 calculations were conducted on the acetyl derivative of **5** because **7** had too many heavy atoms. Both types of calculations were conducted on an Cache™ workstation with the following software versions: MM2, v2.7; AM1, v6.1.

(29) We thank Mr. Y. Moon for conducting this experiment.

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allowed to cool to ambient temperature and was partitioned between H_2O (50 mL) and CH_2Cl_2 (250 mL). The layers were separated, and the organic layer was washed with H_2O (50 mL), 1 M HCl (3 × 25 mL), saturated aqueous $NaHCO_3$ (2 × 25 mL), and brine (50 mL), dried over Na_2SO_4, and evaporated to give **4** as a cream colored solid (2.84 g, 101% mass balance): mp 254–55 °C; IR (KBr) 3336, 3184, 3099, 2968, 2929, 1722, 1684, 1496, 1209, 752 cm^{-1}; ^1H NMR δ 1.31 (s, 6), 1.37 (s, 3), 1.39 (d, 2, J = −14.4), 1.45 (d, 2, J = −13.4), 2.05 (d, 1, J = −13.3), 2.69 (d, 2, J = −14.4), 6.91 (ddd, 1, J = 7.2, 1.5), 7.09 (dd, 1, J = 7.2, 1.5), 7.12 (dd, 1, J = 7.2, 1.5), 7.23 (ddd, 1, J = 7.2, 7.2, 1,5), 7.50 (br s, 1), 7.73 (br s, 1).

***endo*-(±)-7-(2-Benzoxazolyl)-1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one (5).** To a stirred solution of the above imide amide **4** (2.84 g, 8.60 mmol) in MeOH (500 mL) at 0 °C was added solid $NaBH_4$ (12.5 g, 330 mmol) in portions over 2 h (vigorous evolution of H_2). The mixture was stirred at 0 °C for 6 h after the addition was complete and then placed in a 0 °C refrigerator for 12 h. The reaction mixture was poured into cold H_2O (1 L) and extracted with $CHCl_3$ (6 × 100 mL). The aqueous layer was acidified to ~pH 3–4 with concentrated HCl, saturated with solid NaCl, and extracted with additional $CHCl_3$ (4 × 100 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ and brine (100 mL each), dried over Na_2SO_4, and evaporated to give a cream colored solid (2.95 g, 104% mass balance): ^1H NMR δ 0.95 (d, 1, J = −15.1), 1.08 (s, 3), 1.21 (s, 3), 1.36 (d, J = −13.2), 1.36 (s, 3), 1.52 (d, 1, J = −15.0), 1.81 (d, 1, J = −13.4), 2.35 (d, 1, J = −15.0), 2.88 (d, 1, J = −15.1), 4.55–4.62 (m, 1), 5.21–5.35 (m, 1), 5.80 (br s, 1), 6.81–6.87 (m, 1), 6.95–6.98 (m, 1), 7.07–7.12 (m, 1), 7.28 (br s, 1), 7.69 (br s, 1); ^{13}C NMR δ 24.33, 27.14, 32.39, 36.04, 38.63, 39.15, 43.52, 44.16, 45.98, 84.86, 118.34, 120.29, 124.26, 125.17, 127.43, 149.89, 176.58, 177,54; MS calcd for $C_{18}H_{24}N_2O_4$ 332.1736, found 332.1736.

A portion (2.50 g, 7.52 mmol) of this crude solid was dissolved in CF_3CO_2H (25 mL), and triethylsilane (9.5 mL, 6.90 g, 59.3 mmol) was added. The brown mixture was stirred rapidly at room temperature for 7 h, resulting in a green solution. The mixture was diluted with CH_2Cl_2 (250 mL), and saturated aqueous $NaHCO_3$ (100 mL) was added carefully (vigorous foaming!); solid $NaHCO_3$ was added until the gas evolution had ceased and the aqueous layer was basic. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and evaporated to give an off-white solid (2.10 g, 88%): ^1H NMR δ 1.01 (s, 3), 1.03 (d, 1, J = −12.8), 1.26 (s, 3), 1.32–1.36 (m, 1), 1.33 (s, 3), 1.47 (d, 1, J = −15.1), 1.80 (d, 1, J = −12.9), 2.27 (d, 1, J = −15.3), 2.81 (d, 1, J = −14.1), 3.02 (d, 1, J = −11.7), 3.20 (d, 1, J = −11.9), 5.51 (br s, 1), 6.84–6.90 (m, 1), 6.97–7.00 (m, 1), 7.07–7.13 (m, 1), 7.29–7.34 (m, 1), 8.48 (br s).

The above lactam amide (2.1 g, 6.6 mmol) was suspended in C_6H_6 (35 mL), and pyridine (3.5 mL, 3.42 g, 34.3 mmol) and $SOCl_2$ (2.5 mL, 4.08 g, 34.3 mmol) were added. The flask was fitted with a condenser and appropriate gas trap and was heated in an oil bath maintained at 90 °C for 2 h. The reaction mixture was allowed to cool, and the C_6H_6 was concentrated in vacuo. The resulting brown, semisolid residue was partitioned between CH_2Cl_2 (75 mL) and 1 M HCl (25 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine (25 mL each), dried over Na_2SO_4, and evaporated to give a light yellow solid (2.48 g). Purification of this material by flash chromatography (40 × 150 mm column; 1:1 CH_2Cl_2/EtOAc) gave **5** as a pale yellow solid (1.76 g, 89%): IR (KBr) 3207, 3079, 2979, 2959, 2905, 2853, 1670, 1542, 1494, 1456, 1244, 1153, 1078, 741 cm^{-1}; ^1H NMR δ 1.07 (s, 3), 1.21 (s, 3), 1.34 (s, 3), 1.34 (dd, 1, J = −12.7, 1.9), 1.36 (d, 1, J = −13.6), 1.42 (dd, 1, J = −14.1, 1.3), 1.74 (dt, 1, J = −12.8, 1.9), 2.90 (d, 1, J = −11.1), 2.93 (d, 1, J = −14.1), 2.99 (d, 1, J = −14.1), 3.25 (dt, 1, J = −11.6, 2.2), −4.75 (br s, 1), 7.24–7.28 (m, 2), 7.47–7.49 (m, 1), 7.59–7.63 (m, 1); ^{13}C NMR δ 25.01, 29.09, 30.60, 33.30, 37.52, 38.24, 45.00, 45.85, 47.04, 52.58, 110.70, 119.29, 123.89, 124.18, 141.10, 150.14, 170.94, 174.80; MS calcd for $C_{18}H_{22}N_2O_2$ 298.1681, found 298.1681. Anal. ($C_{18}H_{22}N_2O_2$) C, H, N.

Resolution of 5 via Menthyl Carbamate Derivative. To a stirred solution of *rac*-**5** (447 mg, 1.50 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (0.85 mL, 1.8 M in hexanes, 1.53 mmol) dropwise via syringe. After 0.5 h, (−)-menthyl chloroformate (355 μL, 362 mg, 1.66 mmol) was also added by syringe. The mixture was maintained at −78 °C for 0.5 h and then at 0 °C for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL), and the solvent was concentrated on a rotary evaporator. The residue was partitioned between CH_2Cl_2 (40 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ and brine (10 mL each), dried over $MgSO_4$, and evaporated to give thick oil (887 mg), Separation of the diastereomers by flash chromatography (30 × 160 mm column; 1;1 hexanes/Et_2O) gave the less polar isomer (*R*)-**6** (347 mg), mp 100–02 °C, and mixed fractions (333 mg) containing both diastereomers. These mixed fractions were resubjected to flash chromatography (30 × 150 mm column; 1;1 hexanes/Et_2O) to give an additional 23 mg (370 mg overall; 51%) of the higher R_f material and the more polar isomer (*R*)-**6** (287 mg, 40%), mp 132–33 °C. Less polar diastereomer (*S*)-**6**; IR (KBr) 2957, 2938, 2870, 1711, 1561, 1459, 1270, 1200, 1162, 717 cm^{-1}; ^1H NMR δ −0.03 (q, 1, J = −11.4), 0.58 (d, 3, J = 6.9), 0.75 (d, 3, J = 6.4), 0.81 (d, 3, J = 7.0), 1.14 (s, 3), 1.27 (s, 3), 1.31 (s, 3), 1.54–1.56 (m, 7), 1.82 (d, 1, J = −13.0), 1.88 (m, 1), 2.99 (d, 1, J = −14.4), 3.05 (d, 1, J = −14.0), 3.26 (d, 1, J = −12.6), 3.75 (d, 1, J = −12.0), 4.14 (ddd, 1, J = 10.8, 4,4, 4.4), 7.25 (m, 2), 7.47 (m, 1), 7.59 (m, 1). More polar diastereomer (*R*)-**6**: IR (KBr) 2959, 2870, 1773, 1699, 1430, 1210, 1167, 987, 739 cm^{-1}; ^1H NMR δ 0.49 (d, 3, J = 6.8), 0,52 (q, 1, J = 10.8), 0.80 (d, 3, J = 8.5), 0.86 (d, 3, J = 6.96), 0.82–0.94 (m, 1), 1.13 (s, 3), 1.13–1.77 (m, 7), 1.29 (s, 3), 1.33 (s, 3), 1.80 (d, 1, J = −13.0), 2.96 (d, 1, J = −14.0), 3.06 (d, 1, J = −14.2), 3.12 (dd, 1, J = −12.6, 1.4), 3.76 (dd, 1, J = −12.5, 2.0), 4.15 (ddd, 1, J = 10.8, 4.1, 4.1), 7.27 (m, 2), 7.58 (m, 1).

(1*S*-*endo*)-(−)-7-(2-Benzoxazolyl)-1,5,7-trimethyl-3-azabicyclo-[3.3.1]nonan-2-one (*S*-5). The less polar menthyl carbamate diastereomer (*S*)-**6** (335 mg, 0.70 mmol) was dissolved in CF_3CO_2H (3.5 mL) and allowed to stir for 18 h at ambient temperature. The reaction mixture was partitioned between CH_2Cl_2 (25 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with H_2O, saturated aqueous $NaHCO_3$ (2 × 10 mL each), and brine (10 mL), dried over Na_2SO_4, and evaporated to give an off-white solid (330 mg). Purification of this material by flash chromatography (20 × 150 mm column; 100% EtOAc) gave a white solid (173 mg, 83%); $[\alpha]^{21}_D$ = −7.1° (*c* 2.0, $CHCl_3$).

(1*R*-*endo*)-7-(2-Benzoxazolyl)-1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one (*R*-5). Treatment of (187 mg, 0.39 mmol) the more polar diastereomer (*R*)-**6** with TFA (2 mL) by the aforementioned procedure yielded a pale yellow solid (174 mg). Flash chromatography (15 × 145 mm column; 100% EtOAc) gave a white solid (97 mg, 84%); $[\alpha]^{21}_D$ = +7.4° (*c* 1.95, $CHCl_3$).

[1*R*-[1α,3(*E*),5α,7β]]-4-[7-(2-Benzoxazolyl)-1,5,7-trimethyl-2-oxo-3-azabicyclo[3.3.1]non-3-yl]-4-oxo-2-butenoic Acid, Ethyl Ester (7). To a stirred solution of (*R*)-(+)-**5** (160 mg, 0.54 mmol) in THF (2.7 mL) at −78 °C was added *n*-BuLi (0.42 mL, 1.4 M in hexanes, 0.59 mmol) dropwise by syringe. After 0.5 h at −78 °C, chlorotrimethylsilane (85 μL, 73 mg, 0.67 mmol) was also added in one portion by syringe. The mixture was maintained at −78 °C for 0.5 h and at 0 °C for 0.5 h, and then ethyl fumaryl chloride (110 μL, 120 mg, 0.74 mmol) was added. The cold bath was removed, and the reaction mixture was allowed to stir at ambient temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (1.5 mL), the solvent was concentrated, and the residue was partitioned between EtOAc (15 mL) and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, and evaporated to give an off-white solid (223 mg, 100% mass balance). Purification of this material by flash chromatography (20 × 150 mm column; 70:30 hexanes/EtOAc) gave a white, crystalline solid (184 mg, 83%): mp 138–40 °C; $[\alpha]^{21}_D$ = +76.7°, $[\alpha]^{21}_{578}$ = +79.8°, $[\alpha]^{21}_{546}$ = +90.2° (*c* 1.2, $CHCl_3$); IR (thin film) 2965 (m), 1719 (vs), 1701 (vs), 1678 (vs), 1655 (s), 1560 (s) cm^{-1}; ^1H NMR δ 1.17 (s, 3), 1.28 (s, 3), 1.31 (t, 3, J = 7.1), 1.39 (s, 3), 1.45–1.57 (m, 3), 1.83 (d, 1, J = −13.1), 2.98 (d, 1, J = −14.3), 3.11 (d, 1, J = −14.1), 3.15 (d, 1, J = −13.2), (dd, 1, J = −13.4, 2.5), 4.15–4.20 (m, 2), 5.79 (d, 1, J = 15.4), 6.71 (d, 1, J = 15.4), 7.17–7.21 (m, 2), 7.39–7.42 (m, 1), 7.52–7.55 (m, 2); ^{13}C NMR δ 14.14, 25.69, 29.09, 30.42, 33.39, 37.18, 41.29, 44.71, 46.33, 46.62, 56.23, 60.47, 110.54, 119.67, 124.30, 124.68, 127.34, 136.16, 140.86, 150.21, 164.96, 167.45, 170.39, 176.54; MS calcd for $C_{24}H_{28}N_2O_5$ 424.1998, found 424.1998. Anal. ($C_{24}H_{28}N_2O_5$) C, H, N. Rotation of (*R*)-(−)-enantiomer: $[\alpha]^{21}_D$ = −65.9°.

D-(−)-Fumarate 14. To a stirred solution of D-(−)-camphor sultam **13** (215 mg, 1.00 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (0.55 mL, 2.0 M, 1.10 mmol) dropwise. After 0.5 h at −78 °C, ethyl fumaryl chloride (180 μL, 198 mg, 1.22 mmol) was added dropwise rapidly by syringe. The mixture was maintained at −78 °C for 1 h and at 0 °C for 0.5 h, quenched by the addition of saturated aqueous NH_4Cl (1.5 mL), and concentrated in vacuo. The residue was partitioned between EtOAc (10 mL) and H_2O (3 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, and evaporated to give an orange oil (405 mg). Purification of this material by flash chromatography (20 ×

150 mm column; 70:30 hexanes/EtOAc) gave a white, crystalline solid (191 mg, 56%): mp 119–21 °C; $[\alpha]^{22}_{D} = -93.5°$, $[\alpha]^{22}_{578} = -97.9°$, $[\alpha]^{22}_{546} = -112.5°$ (*c* 1.2, $CHCl_3$); IR (thin film): 2963, 1725, 1682, 1333, 1300, 1181, 1136 cm^{-1}; ^1H NMR δ 0.97 (s, 3), 1.15 (s, 3), 1.30 (t, 3, *J* = 7.1), 1.30–1.46 (m, 2), 1.83–1.95 (m, 3), 2.08–2.13 (m, 2), 3.50 (AB, 2, $J_{AB} = -13.8$, $\nu_{AB} = 20.5$), 3.91–3.97 (m, 1), 4.24 (q, 2, *J* = 7.1), 6.89 (d, 1, *J* = 15,3), 7.52 (d, 1, *J* = 15.3); ^{13}C NMR δ 14.05, 19.81, 20.78, 26,38, 32.78, 38.21, 44.59, 48.72, 52.99, 61.34, 65.06, 132.10, 134.10, 162.46, 164.54; MS calcd for $C_{16}H_{23}NO_5S$ 341.1297, found 341.1297.

Racemic *tert*-Butyl Radical Addition Products 8a–10a. To a boiling solution of *rac*-**7** (67 mg, 0.16 mmol) and 2-iodo-2-methylpropane (38 μL, 59 mg, 0.32 mmol) in C_6H_6 (1.0 mL, 0,16 M) was added a solution of Bu_3SnH (90 μL, 97 mg, 0.33 mmol) and AIBN (6 mg, 0.04 mmol) in C_6H_6 (0.5 mL) by syringe pump over 3 h. After the addition was complete, the solution was heated at reflux an additional 0.5 h; TLC (70:30 hexanes/EtOAc) indicated the presence of some unchanged alkene. An additional portion of Bu_3SnH (90 μL, 97 mg, 0.33 mmol) and AIBN (6 mg, 0.04 mmol) in C_6H_6 (0.5 mL) was added by syringe pump over 3 h and allowed to reflux 0.5 h after the addition; TLC indicated the absence of the starting alkene. The reaction mixture was concentrated, dissolved in of Et_2O (0.5 mL), and stirred vigorously with saturated aqueous KF (0.5 mL) for 2 h. The white solid was removed by filtration through Celite, and the layers were separated. The organic layer was dried over $MgSO_4$ and evaporated to give a clear oil (93 mg, 121% mass balance) that solidified upon standing, VPC and ^1H NMR analysis of the crude mixture indicated a 97;3 mixture of regioisomers and an 80:20 mixture of diastereomers for the major regioisomer. Purification of this material by flash chromatography (15 × 150 mm column; 70:30 hexanes/EtOAc) afforded a clear, glassy oil (49 mg, 64%). Anal. ($C_{28}H_{38}N_2O_5$) C, H, O.

Optically Active *tert*-Butyl Radical Addition Products 8a–9a. [1*S*-[1α,3(*R),5α,7β]]-7-(2-Benzoxazolyl)-α-(1,1-dimethylethyl)-1,5,7-trimethyl-2-dioxo-3-azabicyclo[3.3.1]nonane-3-butanoic Acid, Ethyl Ester.** In a 10-mL round-bottomed flask was placed (*S*)-(−)-**7** (70 mg, 0.165 mmol), *tert*-butylmercuric chloride (73 mg, 0.25 mmol), and a stirring bar, The flask was flushed with Ar, and CH_2Cl_2 (2 mL, 0.08 M) was added. The flask was placed in an ice–water bath and $NaBH_4$ (47 mg, 1.24 mmol) and H_2O (50 μL) were added sequentially, resulting in the precipitation of a black solid. After 1.5 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (10 mL), dried over $MgSO_4$, filtered through Celite, and evaporated to give a glassy residue (75 mg, 94% mass balance). Analysis of the crude reaction mixture by VPC and ^1H NMR spectroscopy indicated a 90:10 ratio of diastereomers. Flash chromatography (15 × 145 mm column; 70;30 hexanes/EtOAc) afforded a clear oil (55 mg, 69%): $[\alpha]^{21}_{D} = +13.8°$, $[\alpha]^{21}_{578} = +14.9°$, $[\alpha]^{21}_{546} = +18.9°$ (*c* 1.48, $CHCl_3$); IR (thin film) 2963, 1734, 1717, 1700, 1684, 1653, 1559, 1456, 1148 cm^{-1}; ^1H NMR δ 0.77 (s, 9), 1.12 (s, 3), 1.14 (t, 3, *J* = 7.1), 1.27 (s, 3), 1.34 (s, 3), 1.36–1.48 (m, 3), 1.76 (d, 1, *J* = −12.9), 2.21 (dd, 1, *J* = 11.5, 2.8), 2.66 (dd, 1, *J* = −15.3, 2.8), 2.89 (d, 1, *J* = −14.3), 3.05 (d, 1, *J* = −12.4), 3.09 (dd, 1, *J* = −12.8, 1.4), 3.70 (dd, 1, *J* = −13.5, 2.3), 3.96 (q, 2, *J* = 7.0), 7.24–7.30 (m, 2), 7.41–7.44 (m, 1), 7.56–7.60 (m, 1); ^{13}C NMR δ 14.18, 26.27, 27.51, 29.74, 30.45, 32.58, 33.39, 37.18, 37.27, 41.42, 44.38, 46.62, 46.95, 51,19, 56.19, 59.47, 110.22, 119.86, 124.49, 124.78, 140.89, 150.27, 170.20, 173.60, 175.83, 176.12; MS calcd for $C_{28}H_{38}N_2O_5$ 482.2781, found 482.2781.

Cyclohexyl Radical Addition Product 8b–9b. [1*R*-[1α,3-(*S),5α,7β]]-7-(2-Benzoxazolyl)-α-cyclohexyl-1,5,7-trimethyl-2-dioxo-3-azabicyclo[3.3.1]nonane-3-butanoic Acid, Ethyl Ester.** Using the foregoing general procedure for the preparation of **8a–9a**, reaction of (*R*)-(+)-**7** (64 mg, 0.15 mmol) with cyclohexylmercuric chloride (144 mg, 0.45 mmol), $NaBH_4$ (85 mg, 2.25 mmol), and H_2O (80 μL, 4.44 mmol) in CH_2Cl_2 (2 mL) at −20 °C (CCl_4/CO_2 bath) gave a crude, glassy product (105 mg). VPC analysis of this crude material indicated a 94:6 mixture of diastereomers. Purification of this material by flash chromatography (15 × 150 mm column; 70:30 hexanes/EtOAc) gave a clear oil (52 mg, 68%): $[\alpha]^{21}_{D} = -11.9°$, $[\alpha]^{21}_{578} = -12.9°$, $[\alpha]^{21}_{546} = -16.4°$ (*c* 2.6, $CHCl_3$); IR (thin film) 2928, 1734, 1716, 1700, 1684, 1653, 1559, 1456, 1148 cm^{-1}; ^1H NMR δ 1.02–1.61 (br m, 15), 1.11 (s, 3), 1.15 (t, 3, *J* = 7.1), 1.26 (s, 3), 1.33 (s, 3), 1.76 (d, 1, *J* = 12.9), 2.11–2.18 (m, 1), 2.68 (dd, 1, *J* = 16.1, 5.0), 2.88 (d, 1, *J* = 14.2), 2.98–3.07 (m, 2), 3.75 (dd, 1, *J* = 13.5, 2.1), 3.97 (q, 2, *J* = 7.1), 7.23–7.28 (m, 2), 7.39–7.42 (m, 1), 7.53–7.56 (m, 1); ^{13}C NMR δ 14.24, 26.18, 26.26, 29.70, 30.45, 30.54, 33.30, 37.28, 38.70, 39.86, 41.42, 44.30, 46.65, 47.03, 56.03, 59.63, 110.29, 119.77, 124.40, 124.68, 140.89, 150.24, 170.20, 173.91, 175.15, 176.12; MS calcd for $C_{30}H_{40}N_2O_5$ 508.2937, found 508.2937. Anal. ($C_{30}H_{40}N_2O_5$) C, H, O.

Hexyl Radical Addition Products 8c–9c. [1*R*-[1α,3(*S),5α,7β]]-7-(2-Benzoxazolyl)-α-hexyl-1,5,7-trimethyl-γ,2-dioxo-3-azabicyclo[3.3.1]-nonane-3-butanoic Acid, Ethyl Ester.** To a stirred solution of (*R*)-(+)-**7** (64 mg, 0.15 mmol) and hexylmercuric bromide (219 mg, 0.60 mmol) in CH_2Cl_2 (2 mL) at −20 °C was added $NaBH_4$ (91 mg, 2.40 mmol) and H_2O (100 μL, 5.55 mmol). After 3 h, TLC (75:25 hexanes/EtOAc) of the reaction mixture indicated the presence of starting material, Additional hexylmercuric bromide (110 mg, 0.30 mmol), $NaBH_4$ (45 mg, 1.19 mmol), and H_2O (50 μL, 2.77 mmol) were added. The mixture was allowed to stir at −20 °C for 1 h; TLC indicated the presence of **7**. The −20 °C bath was replaced with a 0 °C bath, and more hexylmercuric bromide (110 mg, 0.30 mmol), $NaBH_4$ (91 mg, 2.40 mmol), and H_2O (100 μL, 5.55 mmol) were added in two portions over 2 h. The reaction mixture was then diluted with CH_2Cl_2 (7 mL), dried over $MgSO_4$, filtered through Celite, and evaporated to give a clear oil (156 mg). Analysis of the crude mixture by VPC indicated a 82:18 mixture of diasteroemers. Purification of this material by flash chromatography (15 × 150 mm column; 75:25 hexanes/EtOAc) gave 32 mg (42%) of clear oil: $[\alpha]^{21}_{D} = -21.9°$, $[\alpha]^{21}_{578} = -23.2°$, $[\alpha]^{21}_{546} = -28.3°$ (*c* 1.45, $CHCl_3$); IR (thin film) 2930, 2860, 1734, 1696, 1653, 1559, 1456, 1148 cm^{-1}; ^1H NMR (major diastereomer) δ 0.80 (m, 5), 1.05–1,41 (m, 9), 1.12 (s, 3), 1.18 (t, 3, *J* = 7.2), 1.27 (s, 3), 1.34 (s, 3), 1.44 (d, 2, *J* = 13.9), 1.69 (dd, 1, *J* = −16.9, 6.3), 1.77 (d, 1, *J* = 13.1), 2.11–2.17 (m, 1), 2.65 (dd, 1, *J* = −16.9, 6.9), 2.89 (d, 1, *J* = 14.6), 3.03 (d, 2, *J* = 13.8), 3.82 (dd, 1, *J* = 13.5, 2.0), 4.00 (q, 2, *J* = 7.1), 7.23–7.27 (m, 2), 7.38–7.43 (m, 1), 7.54–7.58 (m, 1); ^{13}C NMR (major diastereomer) δ 14.02, 14.23, 22,49, 26.21, 26.89, 29.03, 29.74, 30.45, 31.58, 31.84, 33.23, 37.31, 41.16, 41.29, 44.26, 46.73, 47.08, 55.90, 59.86, 110.38, 119.77, 124,46, 124.75, 140.89, 150.24, 170.20, 174,37, 174.73, 176.22; MS calcd for $C_{30}H_{42}N_2O_5$ 510.3094, found 510.3094.

***tert*-Butyl Radical Addition Products 8d–9d.** Reaction of **14** (34 mg; 0.10 mmol) with *tert*-butylmercuric chloride (44 mg, 0.15 mmol), $NaBH_4$ (28 mg, 0.74 mmol), and H_2O (25 μL, 1.39 mmol) in CH_2Cl_2 (1.25 mL) at 0 °C following the general procedure for **8a–9a** gave a clear oil (40 mg). VPC analysis of this crude material indicated a 65:35 mixture of diastereomers; neither of the regioisomers could be detected, Preparation of authentic samples of these regioisomeric diastereomers is described below. Flash chromatography (10 × 145 mm column; 80:20 hexanes/EtOAc) of this material afforded a fraction (12 mg, 30%) of the major diastereomer and a mixed fraction (18 mg; 45%) containing both diastereomers. Major diastereomer: $[\alpha]^{21}_{D} = -86,4°$, $[\alpha]^{21}_{578} = -90.4°$, $[\alpha]^{21}_{546} = -103.4°$ (*c* = 1.2, $CHCl_3$); ^1H NMR δ 0,95 (s, 3), 0.97 (s, 9), 1.16 (s, 3), 1.25 (t, 3, *J* = 7.1), 1.27–1.42 (m, 2), 1.84–1.90 (m, 3), 2.00–2.04 (m, 2), 2.68 (*A*MX, 1, $J_{AM} = 3.1$, $J_{AX} = 11.7$), 2.77 (A*M*X, 1, $J_{AM} = 3.1$, $J_{MX} = -17.1$), 2.94 (AM*X*, 1, $J_{AX} = 11.7$, $J_{MX} = -17.1$), 3.45 (AB, 2, $J_{AB} = -13.8$, $\nu_{AB} = 21.8$), 3.79–3.85 (m, 1), 4.13 (q, 2, *J* = 7.1); ^{13}C NMR δ 14.24, 19.87, 20,80, 26.44, 27.99, 32.57, 32.74, 33.98, 38.34, 44.56, 47.75, 48.50, 50.80, 52,88, 60.15, 65.10, 170.92, 173.89; MS calcd for $C_{20}H_{33}NO_5S$ 399.2079, found 399.2079.

Preparation of Authentic Racemic Mixtures of 8a and 10a. Ethyl 3,3-Dimethylbutanoate. To a stirred solution of 100% EtOH (6.5 mL, 5.10 g, 0.11 mol) and Et_3N (15.3 mL, 11.1 g, 0.11 mol) in Et_2O (100 mL) at 0 °C was added 3,3-dimethylbutanoyl chloride (14.0 mL, 13.6 g, 0.10 mol) dropwise. The mixture was maintained at 0 °C for 15 min and room temperature for 0.5 h and then was poured into a separatory funnel containing H_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (50 mL), The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine (50 mL each), dried over $MgSO_4$, and evaporated to give 13.8 g of pale yellow liquid. Distillation of this material afforded ethyl 3,3-dimethylbutanoate as a clear liquid (8.40 g, 58%): bp 140–42 °C (lit.[31] bp 144.5–144.7 °C); ^1H NMR δ 1.02 (s, 9), 1.25 (t, 3, *J* = 7.1), 2.18 (s, 2), 4.11 (q, 2, *J* = 7.1).

1-Ethyl 2-(1,1-Dimethylethyl)butanedioate (12a). This procedure is based on that of Petragnani and Yonashiro.[32] A solution of LDA was generated by treating diisopropylamine (3.20 mL, 2.31 g, 22.8 mmol) with *n*-BuLi (12.3 mL, 1.8 M, 22.1 mmol) in THF (20 mL) at 0 °C and stirring for 0.5 h. The flask was cooled to −78 °C, ethyl 3,3-dimethylbutanoate (3.35 mL, 2.99 g, 20.0 mmol) was added rapidly dropwise by syringe, and the mixture was maintained at −78 °C for 1 h. In a separate flask, a solution of iodoacetic acid (3.90 g, 21.0 mmol) in THF (7 mL) was added to a stirred suspension of lithium hydride (200 mg, 25.2 mmol) in THF (13 mL) at 0 °C. After 0.75 h, HMPA (3.5 mL, 3.61 g, 20.1 mmol) was added to the thick suspension of the lithium iodoacetate, resulting in a clear, yellow solution. This solution was added dropwise to the solution of the enolate at −78 °C. The mixture was maintained at −78 °C for 1 h, 0 °C for 2 h, and at ambient temperature for 16 h. The reaction was quenched by the addition of 3 M HCl saturated with solid NaCl (25 mL). This mixture was poured into a separatory funnel containing additional 3 M HCl saturated with NaCl (40 mL) and was extracted with Et_2O (4 × 50 mL). The combined organics were washed with 1 M HCl saturated with NaCl (3 × 50 mL), brine (50 mL), saturated $Na_2S_2O_3$ (50 + 25 mL), and brine (50 mL), dried over Na_2SO_4,

and evaporated to give a yellow liquid (4.51 g). Distillation of this material yielded an orange liquid (1.75 g, 43%), bp 107–110 °C at 0.15 mmHg: IR (thin film) 2967, 1728, 1181, 1159 cm^{-1}; ^1H NMR δ 0.97 (s, 9), 1.26 (t, 3, J = 7.1), 2.52 (*A*MX, 1, J_{AM} = 3.1, J_{AX} = −16.6), 2.60 (A*M*X, 1, J_{AM} = 3.1, J_{MX} = 11.5), 2.84 (AM*X*, 1, J_{AX} = −16.6, J_{MX} = 11.5), 4.16 (q, 2, J = 7.1); ^{13}C NMR δ 14.13, 27.76, 32.52, 50.99, 60.30, 173.86, 179.03; MS calcd for $C_{10}H_{18}O_4$ 202.1205, found 202.1205.

The acid chloride of **12a** was prepared by heating a solution of **12a** (215 mg, 1.06 mmol) and $SOCl_2$ (0.5 mL, 816 mg, 6.86 mmol) in C_6H_6 (1 mL) at reflux for 1.5 h. Upon cooling, the solvent was evaporated, and the brown liquid was pumped under high vacuum for 1 h and then used without further purification: ^1H NMR δ 0.98 (s, 9), 1.27 (t, 3, J = 7.1), 2.66 (*A*MX, 1, J_{AM} = 3.0, J_{AX} = 11.5), 3.05 (A*M*X, 1, J_{AM} = 3.0, J_{MX} = −18.2), 3.39 (AM*X*, 1, J_{AX} = 11.5, J_{MX} = −18.2), 4.17 (q, 2, J = 7.1).

***rac*-8a.** To a stirred solution of *rac*-**5** (22 mg, 0.075 mmol) in 0.5 mL of THF at −78 °C was added *n*-BuLi (46 μL, 1.8 M, 0.083 mmol) dropwise. After 15 min, the flask was removed from the cold bath for 5 min and returned to the bath for another 10 min. The acid chloride of **12a** (20 μL, 22 mg, 0.10 mmol) was added in one portion. The mixture was maintained at −78 °C for 0.5 h and at 0 °C for 0.5 h, then was quenched by the addition of saturated aqueous NH_4Cl (10 drops), and concentrated. The crude residue was partitioned between Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (3 mL). The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine (3 mL each), dried over $MgSO_4$, and evaporated to give a semisolid residue (37 mg). Purification of this material by flash chromatography (10 × 150 mm column; 70:30 hexanes/EtOAc) gave a clear oil (18 mg) that was a 60:40 mixture of diastereomers: ^1H NMR (major diastereomer) δ 0.78 (s, 9), 1.13 (s, 3), 1.15 (t, 3, J = 7.2), 1.28 (s, 3), 1.35 (s, 3), 1.43–1.47 (m, 2), 1.75–1.79 (d, 1, J = −12.8), 2.23 (dd, 1, J = 11.4, 2.9), 2.67 (dd, 1, J = −15.3, 2.8), 2.86–3.12 (m, 3), 3.71 (dd, 1, J = 13.5, 2.4), 3.97 (q, 2, J = 7.1), 7.26–7.32 (m, 2), 7.40–7.47 (m, 1), 7.53–7.68 (m, 1). ^1H NMR (minor diastereomer) δ 0.71 (s, 9), 1.13 (s, 3), 1.18 (t, 3, J = 7.2), 1.28 (s, 3), 1.35 (s, 3), 1.43–1.52 (m, 2), 1.71–1.79 (m, 2), 1.92 (dd, 1, J = −18.9, 2.8), 2.86–3.12 (m, 3), 3.89–3.94 (m, 1), 3.97 (q, 2, J = 7.1), 7.19–7.26 (m, 2), 7.40–7.47 (m, 1), 7.53–7.68 (m, 1).

1,1-Dimethylethyl 3,3-Dimethylbutanoate. The following esterification is based on a literature procedure.[33] A 100-mL, round-bottomed flask was charged with 2-methyl-2-propanol (8.80 mL, 6.92 g, 93 mmol), *N*,*N*-dimethylaniline (13.1 mL, 12.5 g, 103 mmol), and Et_2O (20 mL), and then the flask was fitted with a Claisen head equipped with a dropping funnel and a condenser. A solution of 3,3-dimethylbutanoyl chloride (13.0 mL, 12.6 g, 94 mmol) in Et_2O (5 mL) was transferred to the dropping funnel and then added to the flask dropwise. After the addition was complete, the flask was immersed in an oil bath maintained at 50 °C and was heated for 12 h; two layers formed after 0.5 h. The mixture was allowed to cool, resulting in the crystallization of the lower layer. H_2O (25 mL) was added to dissolve the solid, and the layers were separated. The organic layer was diluted with Et_2O (25 mL) and was washed with 1 M H_2SO_4 (10-mL portions, until the washings did not become cloudy when made alkaline), saturated aqueous $NaHCO_3$, and brine (25 mL each), dried over $MgSO_4$, and evaporated to give 14.4 g of clear liquid. Distillation of this liquid provided 1,1-dimethylethyl 3,3-dimethylbutanoate as a clear liquid (10.4 g, 65%): bp 158–60 °C; ^1H NMR δ 1.02 (s, 9), 1.45 (s, 9), 2.09 (s, 2).

1-Ethyl 3-(1,1-Dimethylethyl)butanedioate (12b). A solution of LDA was generated by treating diisopropylamine (5.20 mL, 3.75 g, 37.1 mmol) with *n*-BuLi (20.0 mL, 1.8 M, 36.0 mmol) in THF (30 mL) at 0 °C and stirring for 0.5 h. The flask was cooled to −78 °C and a solution of 1,1-dimethylethyl 3,3-dimethylbutanoate (5.17 g, 30.0 mmol) in THF (5 mL) was added rapidly dropwise by syringe over 2 min. The mixture was maintained at −78 °C for 15 min, 0 °C for 0.5 h, and then returned to −78 °C for 0.5 h. In a separate flask, a solution of iodoacetic acid (6.14 g, 33.0 mmol) in THF (10 mL) was added to a stirred suspension of lithium hydride (362 mg, 45.5 mmol) in THF (20 mL) at 0 °C. After 15 min, HMPA (3.5 mL, 3.61 g, 20.1 mmol) was added to the thick suspension of the lithium iodoacetate, resulting in a clear, yellow solution. This solution was maintained at 0 °C for 15 min and then was added dropwise to the solution of the enolate at −78 °C. The mixture was maintained at −78 °C for 1 h and at ambient temperature for 16 h. The reaction was quenched by the addition of 3 M HCl saturated with solid NaCl (40 mL). This mixture was poured into a separatory funnel and was extracted with Et_2O (4 × 60 mL). The combined organics were washed with 1 M HCl saturated with NaCl (3 × 60 mL), brine (60 mL), saturate $Na_2S_2O_3$ (2 × 60 mL), and brine (60 mL), dried over Na_2SO_4, and evaporaed to give a yellow liquid (7.94 g). Evacuation of this material under high vacuum removed volatile impurities (mostly, 1,1-dimethylethyl 3,3-dimethylbutanoate) and gave the half-ester 1-(1,1-dimethylethyl) 2-(1,1-dimethylethyl)butanedioate as a pale yellow liquid (5.87 g, 85%) that was used without further purification: ^1H NMR δ 0.97 (s, 9), 1.44 (s, 9), 2.48 (*A*MX, 1, J_{AM} = 3.2, J_{AX} = −17.6), 2.49 (A*M*X, 1, J_{AM} = 3.2, J_{MX} = 12.7), 2.77 (AM*X*, 1, J_{AX} = −17.6, J_{MX} = 12.7).

A stirred solution of the above half-ester (5.87 g, 25.5 mmol) and 100% EtOH (1.65 mL, 1.30 g, 28.2 mmol) in Et_2O (100 mL) was treated with 4-(dimethylamino)pyridine (312 mg, 2.55 mmol) and *N*,*N*-dicyclohexylcarbodiimide (5.78 g, 28.0 mmol).[34] The reaction was allowed to stir for 5 h and filtered. The filtrate was washed with H_2O (3 × 50 mL), 5% HOAc (3 × 60 mL), and H_2O, saturated aqueous $NaHCO_3$, and brine (60 mL each), dried over $MgSO_4$, and evaporated to give a brown liquid (6.57 g). Distillation of this material yielded 1-(1,1-dimethylethyl)-4-ethyl 2-(1,1-dimethylethyl)butanedioate as a clear liquid (4.40 g, 67%): bp 145–150 °C at 27 mmHg; IR (thin film) 2969, 1738, 1370, 1150 cm^{-1}; ^1H NMR δ 0.97 (s, 9), 1.24 (t, 3, J = 7.1), 1.45 (s, 9), 2.42 (*A*MX, 1, J_{AM} = 3.0, J_{AX} = −15.9), 2.51 (A*M*X, 1, J_{MX} = 11.6), 2.71 (AM*X*, 1, J_{AX} = −15.9, J_{MX} = 11.6), 4.11 (q, 2, J = 7.0); ^{13}C NMR δ 14.12, 27.80, 27.96, 32.45, 32.94, 51.99, 60.37, 80.24, 172.69, 173.01.

To a stirred solution of the above diester (1.29 g, 4.99 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (3.9 mL, 5.77 g, 50.6 mmol), and the mixture was allowed to stand for 18 h. The reaction was diluted with CH_2Cl_2 (50 mL) and was washed with H_2O (3 × 15 mL) and brine (15 mL), dried over Na_2SO_4, and evaporated to give **12b** as an off-white oil (987 mg; 98%): IR (thin film) 2968, 1738, 1709, 1374, 1188, 1163 cm^{-1}; ^1H NMR: δ 1.01 (s, 9), 1.24 (t, 3, J = 7.1), 2.50 (*A*MX, 1, J_{AM} = 2.2, J_{AX} = −15.7), 2.66 (A*M*X, 1, J_{AM} = 2.2, J_{MX} = 11.7), 2.76 (AM*X*, 1, J_{AX} = −15.7, J_{MX} = 11.7), 4.13 (q, 2, J = 7.1); ^{13}C NMR δ 14.02, 27.78, 32.42, 32.75, 51.22, 60.73, 172.53, 180.02; MS calcd for $C_{10}H_{16}O_3$ (M − H_2O) 184.1099, found 184.1099.

The acid chloride of **12b** was prepared by heating a stirred solution of **12b** (121 mg, 0.60 mmol) and $SOCl_2$ (0.3 mL, 489 mg, 4.11 mmol) in C_6H_6 (1.5 mL) at 85 °C for 1 h. The solvent was removed on a rotary evaporator, and the residue was dissolved in C_6H_6 (1 mL) and evaporated again to give a yellow-orange oil (120 mg, 91%) that was used without further purification: ^1H NMR δ 1.06 (s, 9), 1.27 (t, 3, J = 7.2), 2.59 (*A*MX, 1, J_{AM} = −17.1, J_{AX} = 3.3), 2.84 (A*M*X, 1, J_{AM} = −17.1, J_{MX} = 11.5), 3.15 (AM*X*, 1, J_{AX} = 3.3, J_{MX} = 11.5), 4.17 (q, 2, J = 7.1).

***rac*-10a.** To a stirred solution *rac*-**5** (22 mg, 0.074 mmol) in THF (0.5 mL) at −78 °C was added *n*-BuLi (50 μL, 1.8 M, 0.09 mmol) dropwise. After 0.5 h, a solution of the acid chloride of **12b** (21 mg, 0.095 mmol) in THF (0.5 mL) was added rapidly by syringe. The mixture was maintained at −78 °C for 0.5 h and at 0 °C for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 drops) and concentrated in vacuo. The residue was partitioned between Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (3 mL) and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 mL), dried over $MgSO_4$, and evaporated to give a yellow oil (34 mg). Purification of this oil by flash chromatography (10 × 150 mm column; 1:1 hexanes/Et_2O) afforded a less polar fraction (11 mg, 31%) containing one diastereomer, a mixed fraction (4 mg, 11%) containing both diastereomers, and a polar fraction (8 mg, 22%) containing the other diasteromer: ^1H NMR (less polar) δ 0.41 (s, 9), 0.97 (s, 3), 1.17 (t, 3, J = 7.1), 1.18 (s, 3), 1.30–1.33 (m, 1), 1.34 (s, 3), 1.43 (d, 2, J = −14.9), 1.87 (d, 1, J = −12.6), 2.25 (*A*MX, 1, J_{AM} = −16.7, J_{AX} = 2.8), 2.54 (A*M*X, 1, J_{AM} = −16.7, J_{MX} = 12.2), 2.94 (d, 1, J = −14.5), 3.04 (d, 1, J = −13.8), 3.22 (d, 1, J = −13.4), 3.61 (AM*X*, 1, J_{AX} = 2.8, J_{MX} = 12.2), 2.90 (dd, 1, J = −11.8, J = 1.0), 3.99 (q, 2, J = 7.1), 7.16–7.23 (m, 2), 7.40–7.44 (m, 1), 7.52–7.57 (m, 1); ^1H NMR (more polar) δ 0.71 (s, 9), 1.16 (s, 3), 1.20 (t, 3, J = 7.2), 1.29 (s, 3), 1.35 (s, 3), 1.36–1.41 (m, 1), 1.41 (d, 2, J = −14.2), 1.72 (d, 1, J = −13.0), 2.02 (dd, 1, J = −16.7, J = 8.5), 2.91 (d, 2, J = −13.4), 3.04 (d, 1, J = −13.8), 3.93 (q, 2, J = 7.1), 4.08–4.15 (m, 2), 7.15–7.23 (m, 2), 7.43–7.47 (m, 1), 7.55–7.60 (m, 1).

Preparation of Authentic Samples of Camphor Sultam Radical Addition Diastereomers. *rac*-8d. To a stirred solution of D-(−)-camphor sultam **13** (21.5 mg, 0.10 mmol) in THF (0.5 mL) at −78 °C was added *n*-BuLi (55 μL, 2.0 M, 0.11 mmol) dropwise by syringe. After 0.5 h at −78 °C, the acid chloride of **11** (40 μL, 44 mg, 0.20 mmol) was added rapidly in one portion. The mixture was maintained at −78 °C for 1 h and 0 °C for 0.5 h and then was quenched by the addition of saturated aqueous NH_4Cl (15 drops). The THF was concentrated in vacuo, and the residue was partitioned between Et_2O (10 mL) and H_2O (1 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, and evaporated to give a brown oil (40 mg) that was an approximately 1:1 mixture of diastereomers.

***rac*-10d.** Using the foregoing procedure for **8d–9d**, reaction of D-(−)-camphor sultam **13** (21 mg, 0.10 mmol) with *n*-BuLi (55 μL, 2.0 M,

0.11 mmol), and the acid chloride of **12b** (35 mg, 0.16 mmol) yielded a clear, glassy oil (34 mg) that was an approximately 1:1 mixture of diastereomers.

Hydrolytic Cleavage of Radical Addition Products. (*S*)-(+)-1-Ethyl 2-(1,1-Dimethylethyl)butanedioate (15a). To a stirred solution of **8a–9a** (55 mg, 0.11 mmol) in THF (1.65 mL, *not* distilled) was added H_2O (0.5 mL, 0.05 M overall). The flask was immersed in an ice–water bath, and 30% H_2O_2 (55 μL, 0,55 mmol) and $LiOH·H_2O$ (6 mg, 0.14 mmol) were added sequentially. The cold bath was removed, and the mixture was allowed to stir at room temperature for 18 h. The flask was again cooled to 0 °C and 1.5 M aqueous Na_2SO_3 (0.44 mL, 0.66 mmol) was added, followed by saturated aqueous $NaHCO_3$ (0,5 mL). The THF was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and H_2O (12 mL each). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 12 mL). The combined organics were dried over $MgSO_4$ and evaporated to give a white solid (32 mg, 97% mass balance). Purification of this solid by flash chromatography (10 × 150 mm column, 100% EtOAc) yielded the pure auxiliary (*S*)-(−)-**5** (27 mg, 82%). The aqueous layer was acidified to ~pH 1 with 6 M HCl, saturated with solid NaCl, and extracted with EtOAc (4 × 10 mL). The combined organics were dried over Na_2SO_4 and evaporated to give a pale yellow oil (21 mg, 95%): $[\alpha]^{21}_D$ = +14.1°, $[\alpha]^{21}_{578}$ = +14.7°, $[\alpha]^{21}_{546}$ = +17.0° (*c* 1.3, $CHCl_3$); IR (thin film) 2967, 1728, 1181, 1159 cm^{-1}; ^1H NMR δ 0.97 (s, 9), 1.26 (t, 3, *J* = 7.1), 2.52 (*AMX*, 1, J_{AM} = 3.1, J_{AX} = −16.6), 2.60 (A*M*X, 1, J_{AM} = 3.1, J_{MX} = 11.5), 2.84 (AM*X*, 1, J_{AX} = −16.6, J_{MX} = 11.5), 4.16 (q, 2, *J* = 7.1); ^{13}C NMR δ 14.13, 27.76, 32.52, 50.99, 60,30, 173.86, 179.03; MS calcd for $C_{10}H_{18}O_4$ 202.1205, found 202.1205.

(*R*)-(−)-1-Ethyl 2-Cyclohexylbutanedioate (15b). Hydrolysis of **8b–9b** (52 mg, 0.10 mmol) using the procedure for the preparation of (*S*)-(+)-**15a** yielded pure (*R*)-(+)-**5** (24 mg, 83%) and (*R*)-(−)-**15b** (20 mg, 87%) as a pale yellow oil; $[\alpha]^{21}_D$ = +14.1°, $[\alpha]^{21}_{578}$ = +14.7°, $[\alpha]^{21}_{546}$ = −20.7° (*c* 1.0, $CHCl_3$); ^1H NMR δ 1.01–1.27 (m, 6), 1.24 (t, 3, *J* = 7.1), 1.61–1.75 (m, 5), 2.46 (AM*X*, 1, J_{AX} = −15.8, J_{MX} = 2.4), 2.66–2.73 (m, 1), 2.75 (*AMX*, 1, J_{AM} = 10.8, J_{AX} = −15.8), 4.15 (q, 2, *J* = 7.1); ^{13}C NMR δ 14.16, 26.08, 26.25, 29.99, 30.52, 33.10, 39.83, 46.72, 60.50, 174.28, 178.71; MS calcd for $C_{12}H_{21}O_4$ (M + H) 229.1440, found 229.1440.

(*R*)-(−)-Diethyl 2-Cyclohexylbutanedioate (16b). To a stirred solution of (*R*)-(−)-**15b** (20 mg, 0.09 mmol) in C_6H_6 (0.5 mL) was added *N,N*-dimethylformamide diethyl acetal (25 μL, 21 mg, 0.14 mmol). The mixture was heated at 80 °C for 4 h, allowed to cool to room temperature, diluted with Et_2O (10 mL), and transferred to a separatory funnel. The organic layer was washed with 2 M aqueous HCl (3 × 2 mL), H_2O (2 mL), saturated aqueous $NaHCO_3$ (3 × 2 mL), and brine (2 mL), dried over $MgSO_4$, and evaporated to give a pale yellow oil (17 mg, 74%). The ^1H NMR spectrum of the material indicated the presence of ~5% of the monomethyl ester: $[\alpha]^{21}_D$ = −10.6°; ^1H NMR δ 0.97–1.20 (m, 6), 1.23 (t, 3, *J* = 7.1), 1.25 (t, 3, *J* = 7.1), 1.52–1.75 (m, 5), 2.37–2.47 (m, 1), 2.64–2.75 (m, 2), 4.10 (q, 2, *J* = 7.1), 4,10–4.19 (m, 2); ^{13}C NMR δ 14.11, 14.21, 26.14, 26.27, 30.06, 30.55, 33.46, 39.93, 47.01, 60.29, 60.47, 172.50, 174.44; MS calcd for $C_{12}H_{19}O_3$ (M − OEt) 211.1334, found 211.1334.

(*S*)-(−)-1-Ethyl 2-Hexylbutanedioate (15c). Hydrolysis of **8c–9c** (32 mg, 0.06 mmol) using the procedure for the preparation of (*S*)-(+)-**15a** gave pure (*R*)-(+)-**5** (16 mg, 89%) and (*S*)-(−)-**15c** (11 mg, 79%) as a pale yellow oil: $[\alpha]^{21}_D$ = −11.2°, $[\alpha]^{21}_{578}$ = −11.6°, $[\alpha]^{21}_{546}$ = −13.4° (*c* 1.1, $CHCl_3$); IR (thin film) 2930, 1734, 1711, 1177 cm^{-1}; ^1H NMR δ 0.85–0.89 (m, 3), 1.09–1.38 (m, 8), 1.25 (t, 3, *J* = 7.1), 1.42–1.63 (m, 2), 2.43–2.51 (m, 1), 2.71–2.84 (m, 2), 4.15 (q, 2, *J* = 7.1); ^{13}C NMR δ 14.02, 14.14, 22.52, 26.76, 28.99, 31.55, 31.81, 35.66, 40.93, 60.66, 174.89, 178.13; MS calcd for $C_{12}H_{20}O_3$ (M − H_2O) 212.1412, found 212.1412.

(*S*)-(−)-Diethyl 2-Hexylbutanedioate (16c). Following the procedure for the preparation of (*R*)-(−)-**16b**, reaction of (*S*)-(−)-**15c** (11 mg, 0.05 mmol) afforded (*S*)-(−)-**16c** (10 mg, 77%) as a pale yellow oil, that was identical by ^1H NMR spectroscopy to that prepared from (*S*)-(−)-hexylsuccinic acid (vide infra): $[\alpha]^{21}_D$ = −7.4°, $[\alpha]^{21}_{578}$ = −7.6°, $[\alpha]^{21}_{546}$ = −8.9° (*c* 1.0, $CHCl_3$).

Preparation of Authentic Samples of Optically Active Alkylsuccinates. (*R*)-(−)-Diethyl 2-(1,1-Dimethylethyl)butanedioate (16a). To a stirred suspension of (*R*)-(−)-2-(1,1-dimethylethyl)butanedioic acid[20a] (348 mg, 2.00 mmol) in C_6H_6 (10 mL) was added *N,N*-dimethylformamide diethyl acetal (1,00 mL, 859 mg, 5.83 mmol). The mixture was heated at reflux for 4 h, cooled to ambient temperature, and diluted with Et_2O (120 mL). The organic layer was washed with 2 M aqueous HCl (3 × 20 mL), H_2O (20 mL), saturated aqueous $NaHCO_3$ (4 × 15 mL), H_2O (2 × 15 mL), and brine (15 mL), dried over $MgSO_4$, and evaporated to give a clear liquid (418 mg). Purification of this material by flash chromatography (20 × 140 mm column; 90:10 hexanes/EtOAc) yielded a clear liquid (382 mg, 83%). ^1H NMR of this substance indicated the presence of ~5% of the dimethyl ester: $[\alpha]^{21}_D$ = −12.3°, $[\alpha]^{21}_{578}$ = −13.1°, $[\alpha]^{21}_{546}$ = −15.2° (*c* 1.8, $CHCl_3$); IR (thin film) 2969, 1736, 1159 cm^{-1}; ^1H NMR δ 0.97 (s, 9), 1.23 (t, 3, *J* = 7.1), 1.27 (t, 3, *J* = 7.1), 2.47 (*AMX*, 1, J_{AM} = 2.9, J_{AX} = −16.2), 2.61 (A*M*X, 1, J_{AM} = 2.9, J_{MX} = 11.8), 2.78 (AM*X*, 1, J_{AX} = −16.2, J_{MX} = 11.8), 4.07–4.19 (m, 2); ^{13}C NMR δ 14.02, 14.14. 27.70, 32.46, 32.78, 51.15, 60.05, 60.44, 172.53, 174.01.

(*R*)-(−)-1-Ethyl 2-(1,1-Dimethylethyl)butanedioate (15a). A stirred solution of (*R*)-(−)-**16a** (230 mg, 1.00 mmol) in 100% EtOH (1.5 mL) was treated with 6 M KOH (210 μL, 1.26 mmol) and then heated at reflux for 1 h and allowed to cool. The EtOH was concentrated, and the residue was dissolved in H_2O (10 mL) and extracted with Et_2O (4 × 10 mL), The combined organic layers were dried over $MgSO_4$ and evaporated to give a clear oil (3 mg) that was determined to be (*R*)-(−)-**16a** by ^1H NMR spectroscopy. The aqueous layer was acidified to pH 0–1 with concentrated HCl, saturated with solid NaCl, and extracted with Et_2O (5 × 10 mL). The combined organics were dried over Na_2SO_4 and evaporated to give (*R*)-(−)-**15a** as a cloudy oil (141 mg, 70%): $[\alpha]^{21}_D$ = −17.2°, $[\alpha]^{21}_{578}$ = −18.3°, $[\alpha]^{21}_{546}$ = −21.3° (*c* 1.95, $CHCl_3$).

(*S*)-(+)-Diethyl 2-Cyclohexylbutanedioate (16b). Reaction of (*S*)-(+)-2-cyclohexylbutanedioic acid[20b] (30 mg, 0.15 mmol) and *N,N*-dimethylformamide diethyl acetal (57 μL, 49 mg, 0.33 mmol) following the procedure for the preparation of (*R*)-(−)-**16a** afforded a clear oil (23 mg, 82%) that was not purified further. Analysis of the ^1H NMR spectrum indicated ~5% of the dimethyl ester was present: $[\alpha]^{21}_D$ = +14.9°, $[\alpha]^{21}_{578}$ = +15.6°, $[\alpha]^{21}_{546}$ = +18.1° (*c* 2.3, $CHCl_3$).

(*S*)-(−)-Diethyl 2-Hexylbutanedioate (16c). Reaction of (*S*)-(−)-2-hexylbutanedioic acid[20c] (30 mg, 0.15 mmol) and *N,N*-dimethylformamide diethyl acetal (77 μL, 66 mg, 0.45 mmol) following the procedure for the preparation of (*R*)-(−)-**16a** afforded a clear oil (24 mg, 62%) that was not purified further. Analysis of the ^1H NMR spectrum indicated ~5% of the dimethyl ester was present: $[\alpha]^{21}_D$ = −13.5°, $[\alpha]^{21}_{578}$ = −14.0°, $[\alpha]^{21}_{546}$ = −16.2° (*c* 1.2, $CHCl_3$); IR (thin film) 2930, 1738, 1161 cm^{-1}; ^1H NMR δ 0.84–0.89 (m, 3), 1.20–1.35 (m, 8), 1.24 (t, 3, *J* = 7.1), 1.25 (t, 3, *J* = 7.1), 1.42–1.67 (br m, 2), 2.41 (*AMX*, 1, J_{AM} = −16.1, J_{AX} = 9.3), 2.68 (A*M*X, 1, J_{AM} = −16.1, J_{MX} = 5.0), 2.74–2.85 (m, 1), 4.12 (q, 2, *J* = 7.2), 4.15 (q, 2, *J* = 7.2); ^{13}C NMR δ 14.01, 14.15, 22.52, 26.83, 29.02, 31.58, 31.94, 35.82, 36.11, 41.19, 41.27, 60.44, 60.50, 172.04, 175.04; MS calcd for $C_{12}H_{21}O_3$ (M − OEt) 213.1491, found 213.1491.

[1α,3(*E*),5α,7β]-[1*S*]-3-[7-(2-Benzoxazolyl)-1,5,7-trimethyl-2-oxo-3-azabicyclo[3.3.1]non-3-yl]-1-oxopropane (17). To a stirred solution of (*S*)-(−)-**5** (149 mg 0.50 mmol) in THF (2.5 mL) at −78 °C was added *n*-BuLi (0.37 mL, 1.4 M, 0.52 mmol) dropwise by syringe. After 0.5 h at −78 °C, freshly distilled propionyl chloride (52 μL, 55 mg, 0.59 mmol) was added rapidly. The mixture was maintained at −78 °C for 0.5 h and at 0 °C for 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 drops), and the THF was concentrated on a rotary evaporator. The residue was partitioned between Et_2O (15 mL) and H_2O (5 mL), and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, and evaporated to give a white solid (177 mg). Flash chromatography (15 × 150 mm column, 1.25:1 hexanes/Et_2O) afforded a white solid (165 mg, 93%): $[\alpha]^{21}_D$ = +37.4°, $[\alpha]^{21}_{578}$ = +39.3°, $[\alpha]^{21}_{546}$ = +47.7° (*c* 0.7, $CHCl_3$); IR (thin film) 2961, 2932, 1696, 1458, 1165, 1146 cm^{-1}; ^1H NMR δ 0.22 (t, 3, *J* = 7.2), 1.10 (s, 3), 1.23 (s, 3), 1.30 (s, 3), 1.38 (dd, 1, *J* = −13.5, 2.2), 1,41 (d, 1, *J* = −12.8), 1.43 (d, 1, *J* = −14.5), 1.59 (dq, 1, *J* = −18.3, 7.1), 1.74 (d, 1, *J* = −12,9), 2.30 (dq, 1, *J* = −18.3, 7.2), 2.89 (d, 1, *J* = −14.3), 3.01 (d, 2, *J* = −14.0), 3.83 (dd, 1, *J* = −13.5, 2.2), 7.18–7.25 (m, 2), 7.37–7.41 (m, 1), 7.52–7.56 (m, 1); ^{13}C NMR δ 8.11, 26.02, 29.42, 30.38, 33.05, 33,43, 37.21, 41.32, 44.43, 46.49, 55.91, 110.39, 119.66, 124.26, 124.59, 140.99, 150.18, 170.52, 175.96, 177.25; MS calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1943.

(*S*)-(−)-[1α,3(*E*),5α,7β]-[1*S*]-3-[7-(2-Benzoxazolyl)-1,5,7-trimethyl-2-oxo-3-azabicyclo[3.3.1]non-3-yl]-2-iodo-3-oxopropane (18). A solution of LDA in THF was generated by stirring diisopropylamine (64 μL, 46 mg, 0.45 mmol) and *n*-BuLi (0.30 mL, 1.4 M, 0.42 mmol) in THF (0.8 mL) at 0 °C for 0.5 h. The flask was cooled to −78 °C, and a solution of (*S*)-(+)-**17** (124 mg, 0.35 mmol) in THF (1.5 mL) was added dropwise by syringe. The mixture was maintained at −78 °C for 1.5 h and then was transferred by cannula at −78 °C to a flask (also at −78 °C) containing iodine (152 mg, 0.60 mmol) in THF (3.5 mL). The dark red solution was maintained at −78 °C for 0.5 h and at 0 °C for 0.5 h. The reaction was quenched by the addition of 1 M HCl (20–30 drops) and was diluted with Et_2O (40 mL). The organic layer was washed with 1 M HCl (2 × 8 mL), H_2O (8 mL), saturated aqueous $Na_2S_2O_3$ (2 × 8 mL), saturated aqueous $NaHCO_3$ (8 mL), and brine (8 mL), dried over $MgSO_4$, and evaporated to give a yellow oil (159 mg). Purification of this material by flash chromatography (15 × 150 mm column; 1.25:1

hexanes/EtOAc) gave a yellow-white solid (125 mg; 74%), mp 128.5–30.5 °C: $[\alpha]^{21}_D$ = −33.3°, $[\alpha]^{21}_{578}$ = −34.8°, $[\alpha]^{21}_{546}$ = −40.2° (*c* 1.6, $CHCl_3$); IR (thin film) 2963, 2928, 1688, 1456, 1165, 1136 cm^{-1}; ^1H NMR δ 0.91 (d, 3, *J* = 6.7), 1.17 (s, 3), 1.32 (s, 3), 1.35 (s, 3), 1.43 (dd, 1, *J* = −13.5, 2.5), 1.46 (d, 1, *J* = −13.9), 1.46 (d, 1, *J* = −13.0), 1.84 (d, 1, *J* = −13.0), 2.93 (d, 1, *J* = −14.2), 3.01 (dd, 1, *J* = −13.6, 1.6), 3.04 (d, 1, *J* = −13.9), 3.96 (dd, 1, *J* = −13.6, 2.4), 4.89 (q, 1, *J* = 6.7), 7.22–7.27 (m, 2), 7.42–7.46 (m, 1), 7.56–7.59 (m, 1); ^{13}C NMR δ 20.78, 22.36, 26.20, 29.67, 30.55, 33.14, 37.37, 41.67, 43.87, 46.66, 47.24, 56.75, 110.52, 119.86, 124.43, 124.85, 140.96, 150.18, 170.27, 173.89, 175.67; MS calcd for $C_{21}H_{25}IN_2O_3$ 480.0910, found 480.0910.

Radical Allylation Product (*S*)-19b. A solution of (*S*)-(−)-**18** (125 mg, 0,26 mmol), allyltributylstannane (161 μL, 172 mg, 0.52 mmol), and AIBN (7.5 mg, 0.05 mmol) in C_6H_6 (0.75 mL, 0.35 M) was degassed by bubbling Ar through the solution for 15 min. The mixture was then heated at 80 °C for 4 h, allowed to cool, and evaporated. The residue was dissolved in Et_2O (10 mL) and treated with 0.1 M I_2 in Et_2O until the color persisted. The solution was washed with saturated aqueous $Na_2S_2O_3$ (5 mL), the layers were separated, and the ether layer was concentrated. This residue was dissolved in Et_2O (1 mL) and stirred with half-saturated aqueous KF (2 mL) for 6 h. The mixture was filtered through Celite, and the solids were washed with Et_2O (10 mL). The layers were separated, and the organic layer was dried over $MgSO_4$ and evaporated to give a white solid (135 mg). Purification of this solid by flash chromatography (15 × 145 mm column; 1.25:1 hexanes/Et_2O) yielded a white solid (39 mg, 38%), mp 107–10 °C: $[\alpha]^{21}_D$ = +80.5°, $[\alpha]^{21}_{578}$ = +84.6°, $[\alpha]^{21}_{546}$ = +99.1° (*c* 1.95, $CHCl_3$); IR (thin film) 2963, 2930, 1696, 1456, 1163, 1144 cm^{-1}; ^1H NMR (major diastereomer) δ 0.03 (d, 3, *J* = 6.6), 1.15 (s, 3), 1.29 (s, 3), 1.34 (s, 3), 1.37–1.46 (m, 3), 1.53–1.79 (m, 2), 2.13–2.21 (m, 1), 2.83–3.07 (m, 4), 3.94 (dd, 1, *J* = −13.5, 2.3), 4.82–4.88 (m, 2), 5.48–5.62 (m, 1), 7.20–7.24 (m, 2), 7.42–7.44 (m, 1), 7.56–7.59 (m, 1); ^{13}C NMR (major diastereomer) δ 15.24, 26.41, 30.02, 30.48, 33.33, 37.41, 38.37, 40.96, 41.54, 44.07, 46.69, 47.10, 55.88, 110.48, 116.08, 119.86, 124.26, 124.69, 136.15, 140.99, 150.41, 170.07, 176.09, 179.81; MS calcd for $C_{24}H_{30}N_2O_3$ 394.2256, found 394.2256.

(*S*)-(+)-2-Methyl-4-pentenoic Acid (20). Hydrolysis of (*S*)-**19b** (39 mg, 0.10 mmol) using the procedure for the preparation of (*S*)-(+)-**15a** yielded (*S*)-(+)-**20** (6 mg, 55%) as a pale yellow oil: $[\alpha]^{21}_D$ = +10.5°, $[\alpha]^{21}_{578}$ = +10.8°, $[\alpha]^{21}_{546}$ = +12.5° (*c* 0.6, $CHCl_3$); ^1H NMR δ 1.19 (d, 3, *J* = 6.9), 2.15–2.25 (m, 1), 2.39–2.49 (m, 1), 2.56 (q, 1, *J* = 6.9), 5.04–5.12 (m, 2), 5.70–5.84 (m, 1).

Ionic Allylation Product (*S*)-19a. A solution of LDA in THF was generated by stirring diisopropylamine (22 μL, 16 mg, 0.16 mmol) and *n*-BuLi (0.10 mL, 1.4 M, 0.14 mmol) in THF (0.3 mL) at 0 °C for 20 min. The flask was cooled to −78 °C and a solution of (*S*)-(+)-**17** (42 mg, 0.12 mmol) in THF (0.3 mL) was added dropwise by syringe. The mixture was maintained at −78 °C for 1 h and 3-iodo-1-propene (25 μL, 46 mg, 0.27 mmol) was added dropwise. After an additional 1 h at −78 °C, the flask was placed in a −20 °C freezer for 12 h. The reaction was quenched at 0 °C by the addition of 1 M HCl (15 drops) and transferred to separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organics were washed with 1 M HCl (3 mL), H_2O (3 mL), saturated aqueous $Na_2S_2O_3$ (2 × 3 mL), saturated aqueous $NaHCO_3$ (3 mL), and brine (3 mL), dried over $MgSO_4$, and evaporated to give a yellow solid (40 mg). Purification of this material by flash chromatography (10 × 175 mm column; 2:1 hexanes/Et_2O) gave 4 mg of (*S*)-(+)-**17** and (*S*)-**19a** as a white solid (24 mg, 56% based on recovered starting material), mp 138–39 °C: $[\alpha]^{21}_D$ = +35.5°, $[\alpha]^{21}_{578}$ = +37.6°, $[\alpha]^{21}_{546}$ = +45.4° (*c* 1.2, $CHCl_3$); IR (thin film) 2965, 2930, 1690, 1456, 1163, 1142 cm^{-1}; ^1H NMR (major diastereomer) δ 0.80 (d, 3, *J* = 6.8), 1.15 (s, 3), 1.22–1.47 (m, 5), 1.28 (s, 3), 1.33 (s, 3), 1.78 (d, 1, *J* = −12.9), 2.74–2.84 (m, 1), 2.92 (d, 1, *J* = −14.3), 3.05 (d, 2, *J* = −13.8), 3.90 (dd, 1, *J* = −13.7, 2.1), 4.70–4.88 (m, 2), 5.10–5.24 (m, 1), 7.21–7.25 (m, 2), 7.42–7.45 (m, 1), 7.56–7.60 (m, 1); ^{13}C NMR δ 16.62, 26.44, 29.99, 30.51, 33.40, 36.33, 37.37, 40.56, 41.61, 44.04, 46.66, 47.01, 56.04, 110.44, 115.92, 119.80, 124.33, 124.81, 136.46, 140.96, 150.35, 170.17, 175.93, 179.89; MS calcd for $C_{24}H_{30}N_2O_3$ 394.2256, found 394.2256.

(*R*)-(−)-2-Methyl-4-pentenoic Acid (20). Hydrolysis of (*S*)-**19a** (23 mg, 0.06 mmol) using the procedure for the preparation of (*S*)-(+)-**15a** yielded (*S*)-(−)-**20** (4 mg, 57%) as a pale yellow oil: $[\alpha]^{21}_D$ = −4.8°, $[\alpha]^{21}_{578}$ = −5.0°, $[\alpha]^{21}_{546}$ = −6.5° (*c* 0.4, $CHCl_3$).

Iodoamide 22. A solution of LDA in THF was generated by stirring diisopropylamine (55 μL, 40 mg, 0.40 mmol) and *n*-BuLi (0.22 mL, 1.6 M, 0.35 mmol) in THF (0.75 mL) at 0 °C for 0.5 h. The flask was cooled to −78 °C, and a solution of **21**[24] (65 mg, 0.30 mmol) in THF (0.75 mL) was added dropwise by syringe. The mixture was maintained at −20 °C (CCl_4/CO_2 bath) for 0.75 h and then was recooled to −78 °C. The yellow-orange solution of the enolate was transferred by cannula at −78 °C to a solution of iodine (130 mg, 0.51 mmol) in THF (3.5 mL) at −78 °C. The dark red solution was maintained at −78 °C for 0.5 h and at 0 °C for 0.5 h and was quenched by the addition of 0.5 M H_3PO_4 (20 drops). The mixture was diluted with Et_2O (30 mL), and the organic layer was washed with 0.5 M H_3PO_4 (2 mL), saturated aqueous $Na_2S_2O_3$ (3 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried over $MgSO_4$, and evaporated to give a yellow oil (73 mg). Purification of this material by flash chromatography (10 × 150 mm column; 1.25:1 CH_2Cl_2/Et_2O) afforded a clear liquid (51 mg, 50%), that was unstable at room temperature and toward visible light: $[\alpha]^{21}_D$ = +85.3° (*c* 2.55, $CHCl_3$); ^1H NMR δ 1.62–1.68 (m, 1), 1.86 (d, 3, *J* = 6.6), 1.88–1.95 (m, 2), 2.08–2.22 (m, 1), 3.07–3.13 (m, 1), 3.26 (s, 3), 3.28–3.34 (m, 2), 3.30 (s, 3), 3.55 (dd, 1, *J* = 9.3, *J* = 3.0), 3.91–3.98 (m, 1), 4.17–4.22 (m, 1), 4.86 (q, 1, *J* = 6.6); ^{13}C NMR δ 18.28, 22.69, 25.43, 26.79, 56.68, 57.82, 58.81, 59.14, 69.08, 75.22, 171.27.

Radical Allylation Product 23. A solution of **22** (51 mg, 0.15 mmol), allyltributylstannane (93 μL, 99 mg, 0.30 mmol), and AIBN (3 mg, 0.02 mmol) in C_6H_6 (0.5 mL, 0.3 M) was heated at 80 °C for 4 h. The solvent was concentrated, and the clear liquid was dissolved in Et_2O (10 mL) and treated with 0.1 M I_2 in Et_2O until the color persisted. The solution was washed with saturated aqueous $Na_2S_2O_3$ (2 × 5 mL) and brine (5 mL) and evaporated. The residue was dissolved in Et_2O (0.5 mL) and stirred with saturated aqueous KF (0.5 mL) for 1 h, The mixture was filtered through Celite, and the solids were washed with Et_2O (10 mL). The combined organics were dried over $MgSO_4$ and evaporated to give a clear oil (34 mg). Flash chromatography (10 × 150 mm column, 80:20 CH_2Cl_2/Et_2O) of this oil yielded a pale yellow oil (21 mg, 55%): IR (thin film) 2930, 1638, 1458, 1420, 1117 cm^{-1}; ^1H NMR δ 1.14 (d, 3, *J* = 6.5), 1.85–2.18 (m, 5), 2.27–2.37 (m, 1), 2.66–2.73 (m, 1), 3.15–3.32 (m, 3), 3.31 (s, 3), 3.33 (s, 3), 3.55 (dd, 1, *J* = 9.2, *J* = 3.1), 3.96–4.03 (m, 1), 4.20–4.25 (m, 1), 4.97–5.08 (m, 2), 5.68–5.77 (m, 1); ^{13}C NMR δ 17.25, 25.10, 26.92, 38.15, 39.93, 56.59, 71.21, 74.35, 116.73, 135.46, 175.53; MS calcd for $C_{14}H_{25}NO_3$ 255.1834, found 255.1834.

(*R*)-(−)-[1α,3(*E*),5α,7β]-4-[7-(2-Benzoxazolyl)-1,5,7-trimethyl-2-oxo-3-azabicyclo[3.3.1]non-3-yl]-4-oxo-2-propenoic Acid (24). To a stirred solution of (*R*)-(+)-**5** (149 mg, 0.50 mmol) and a few small crystals of hydroquinone (<1 mg) in THF (3.3 mL) at 0 °C was added MeMgBr (0.22 mL, 2.35 M, 0.52 mmol). After 10 min at 0 °C, freshly distilled acryloyl chloride (45 μL, 50 mg, 0.55 mmol) was added by syringe in one portion. The mixture was maintained at 0 °C an additional 10 min, then was diluted with Et_2O (10 mL, peroxide free!), washed with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$ (2 mL each), dried over $MgSO_4$, and evaporated to give a foamy residue (188 mg, 107% mass balance). Purification of this material by flash chromatography (15 × 140 mm column, 1:1 hexanes/Et_2O (peroxide free!)) gave a white solid (107 mg, 61%): mp 139.5–40.5 °C; $[\alpha]^{21}_D$ = −17.7° (*c* 3.0, $CHCl_3$); IR (thin film) 2961, 2930, 1686, 1455, 1240, 1186, 1171 cm^{-1}; ^1H NMR: δ 1.15 (s, 3), 1.25 (s, 3), 1.36 (s, 3), 1.41–1.52 (m, 3), 1.79 (d, 1, *J* = −12.8), 2.96 (d, 1, *J* = −14.3), 3.07 (d, 1, *J* = −14.2), 3.16 (dd, 1, *J* = −13.3, 1.4), 3.81 (dd, 1, *J* = −13.4, 2.5), 4.89 (*A*MX, 1, J_{AM} = 1.8, J_{AX} = 10.4), 5.47 (A*M*X, 1, J_{AM} = 1.8, J_{MX} = −16.9), 5.97 (AM*X*, 1, J_{AX} = 10.4, J_{MX} = −16.9), 7.17–7.20 (m, 2), 7.35–7.38 (m, 1), 7.49–7.52 (m, 1); ^{13}C NMR δ 25.92, 29.30, 30.55, 33.65, 37.31, 41.38, 44.94, 46.40, 46.85, 56.33, 110.42, 119.73, 124.23, 125.20, 130.72, 141.25, 150.50, 169.07, 170.56, 176.45; MS calcd for $C_{21}H_{24}N_2O_3$ 352.1787, found 352.1787.

Atom Transfer Annulation Products 25 and 26. A solution of **24** (71 mg, 0.20 mmol), 4-iodo-1-butyne (60 μL, 102 mg, 0.57 mmol), and hexamethylditin (7 μL, 0.02 mmol) in C_6H_6 (0.55 mL, 0.3 M) was placed in a 5 mm NMR tube. The tube was capped, wrapped with Parafilm, and placed in an oil bath maintained at 70 °C. The tube was then irradiated with a sunlamp at a distance of ~15 cm, bringing the temperature of the bath to 80 °C. After 1 h, additional ditin (7 μL, 0.02 mmol) was added, and the tube was heated and irradiated another 1 h. The contents of the tube were allowed to cool, then were transferred to a 5 mL round-bottomed flask, concentrated, and pumped on high vacuum for 1 h. To the flask was added AIBN (2 mg, 0.01 mmol) and a stirring bar, and the flask was flushed with Ar. Tributyltin hydride (80 μL, 86 mg, 0.30 mmol) and C_6H_6 (2.0 mL, 0.1 M) were added, and the flask was fitted with a condenser and heated at 80 °C for 3 h. The mixture was evaporated, dissolved in Et_2O (10 mL), and treated with 0.1 M I_2 in Et_2O until the color persisted. The ethereal solution was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and evaporated to give a yellow oil (165 mg). The ^1H NMR spectrum of the crude material indicated a 71:29 ratio of 5-exo:6-endo regioisomers (**25** and **26**, respectively) and a 99:1 mixture of 5-exo diastereomers. The oil was dissolved in Et_2O (0,5 mL) and vigorously stirred with saturated aqueous KF (0.5 mL) for 1 h. The mixture was filtered through Celite, and the layers were separated. The organic layer was diluted with Et_2O, dried

over $MgSO_4$, filtered through a plug of flash silica gel (5 × 15 mm), and evaporated to give a yellow oil that was nearly tin free by ^1H NMR spectroscopy. Purification of this material by flash chromatography (15 × 150 column; 1.25;1 hexanes/Et_2O) afforded a clear, glassy oil (39 mg, 48%); $[\alpha]^{21}_D = -52.9°$ (c 1.95, $CHCl_3$); IR (thin film) 2959, 1690, 1455, 1244, 1147 cm^{-1}; ^1H NMR δ 1.11-1.18 (m, 1), 1.14 (s, 3), 1.28 (s, 3), 1,33 (s, 3), 1.27-1.46 (m, 6), 1,79 (d, 1, J = -12.9), 2.11-2.17 (m, 2), 2.91 (d, 1, J = -14.2), 3.04 (d, 1, J = -13.9), 3.06 (dd, 1, J = -13.6, 1.4), 3.81-3.87 (m, 1), 3.96 (dd, 1, J = -13.6, 2.3), 4.50 (d, 1, J = 1.9), 4.74 (d, 1, J = 1.8), 7.21-7.25 (m, 2), 7.41-7.46 (m, 1), 7.54-7.60 (m, 1); ^{13}C NMR δ 24.17, 26.40, 30.03, 30.47, 33.27, 37.40, 41.55, 44.01, 46.63, 47.14, 51.64, 56.10, 106.60, 110.48, 119.83, 124.23, 124.64, 128.63, 141.03, 150.43, 152.31, 170,05, 176.06, 177.78; MS calcd for $C_{25}H_{30}N_2O_5$ 406.2256, found 406.2256.

***cis*-2-[(Phenylseleno)methyl]cyclopentanecarboxylic Acid (28).** This procedure is based on that of Smith and co-workers.[26] A solution of diphenyl diselenide (312 mg, 1.00 mmol) in DMF (5 mL) was purged with Ar for 20 min and then $NaBH_4$ (85 mg, 2.25 mmol) was added. The solution was slowly heated in an oil bath to 100 °C, and the lactone **27**[27] (225 mg, 1,78 mmol) in DMF (1.0 mL) was added by syringe. The temperature of the bath was raised to 120 °C and maintained at this temperature for 4 h. The mixture was cooled, diluted with Et_2O (100 mL), washed with 1 M HCl and brine (25 mL each), dried over $MgSO_4$, and evaporated to give a yellow-orange oil (640 mg). Flash chromatography of this oil (20 × 150 mm column, 2:1 hexanes/EtOAc) yielded a pale yellow oil (278 mg, 55%) that crystallized upon standing. ^1H NMR analysis of this material indicated contamination with ~5% of the starting lactone **27**. An analytical sample of **28** was prepared by trituration of the solid with pentane to give a white solid: mp 70-71 °C. IR (thin film) 2953, 1698, 733, 689 cm^{-1}; ^1H NMR δ 1,57-1.72 (m, 2), 1,79-2.07 (m, 4), 2.39-2.51 (m, 1), 2.88 (*A*MX, 1, $J_{AM} = -12.0$, $J_{AX} = 9.6$), 2.91-3.00 (m, 1), 3.16 (A*M*X, 1, $J_{AM} = -12.0$, $J_{MX} = 6.0$), 7.23-7.29 (m, 3), 7.48-7.52 (m, 2); ^{13}C NMR δ 23,49, 28.51, 29.22, 31.55, 43.68, 47.79, 126,79, 129.04, 130.22, 132.49, 181.49; MS calcd for $C_{13}H_{17}O_2Se$ 284,0316, found 284.0316.

Authentic Mixture of Diastereomers of 25. To a stirred solution of the acid **28** (21 mg, 0.075 mmol) in Et_2O (0.5 mL) at 0 °C was added Et_3N (15 μL, 11 mg, 0.11 mmol) and isobutyl chloroformate (10 μL, 10.5 mg, 0.077 mmol) by syringe. After 0.75 h, the mixture was filtered through Celite to remove the $Et_3N{\cdot}HCl$. The solid was washed with a small portion of dry Et_2O, and the combined filtrates were concentrated. In a separate flask, a solution of *rac*-**5** (22 mg, 0.075 mmol) in THF (0.5 mL) at -78 °C was treated with *n*-BuLi (46 μL, 1.8 M, 0.08 mmol) and allowed to stir for 0.5 h at -78 °C. A solution of the above mixed anhydride in THF (0.3 mL) was then added, and the mixture was maintained at -78 °C for 0.5 h and at 0 °C for 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl (10 drops) and concentrated. The residue was partitioned between Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (3 mL). The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine (3 mL each), dried over $MgSO_4$, and evaporated to give a clear glass (37 mg, 88%) that was used without further purification.

The material was dissolved in THF (1.0 mL), cooled to 0 °C, and 30% H_2O_2 (20 μL, 0.20 mmol) was added. The cold bath was removed and the reaction was allowed to stand for 23 h at ambient temperature. The reaction mixture was partitioned between Et_2O (10 mL) and H_2O (3 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (5 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, and evaporated to give a clear oil (30 mg). Purification of this oil by flash chromatography (10 × 160 mm column, 5:2 hexanes/EtOAc) afforded **25** as a clear oil (6 mg, 10%) that consisted of a 2:1 mixture of diastereomers. The minor diastereomer corresponds to the major diastereomer obtained in the radical annulation: ^1H NMR (major diastereomer) δ 1.14-1.21 (m, 1), 1.17 (s, 3), 1.30 (s, 3), 1.35 (s, 3), 1.30-1.49 (m, 6), 1.79 (d, 1, J = -12.9), 2.14-2.20 (m, 2), 2.94 (d, 1, J = -14.2), 3,07 (d, 1, J = -14.5), 3.12 (d, 1, J = -13.8), 3.23 (d, 1, J = 1.7), 3.68-3.74 (m, 1), 3.92 (dd, 1, J = -13.7, 2.2), 4.41 (d, 1, J = 1.4), 7.22-7.26 (m, 2), 7.43-7.48 (m, 1), 7.57-7.62 (m, 1); ^1H NMR (minor diastereomer) δ 1.14-1.21 (m, 1), 1.17 (s, 3), 1.30 (s, 3), 1.35 (s, 3), 1.30-1.49 (m, 6), 1.79 (d, 1, J = -12.9), 2.09-2.15 (m, 2), 2.94 (d, 1, J = -14.2), 3.07 (d, 1, J = -13.9), 3.09 (d, 1, J = -13.6), 3.83-3.89 (m, 1), 3.98 (dd, 1, J = -13.6, 2.3), 4.50 (d, 1, J = 1.9), 4.74 (d, 1, J = 1.8), 7.22-7.26 (m, 2), 7.43-7.48 (m, 1), 7.57-7.62 (m, 1).

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Supplementary Material Available: Full details for the modified preparation of Kemp's triacid, a complete summary of the crystal structure determination of (*S*)-**6**, and a tabulation of the results of MM2 calculations on **7** (24 pages); tables of observed and calculated structure factors (15 pages), Ordering information is given on any current masthead page,

Regioselective Synthesis of Piperidinones by Metal Catalyzed Ring Expansion-Carbonylation Reactions. Remarkable Cobalt and/or Ruthenium Carbonyl Catalyzed Rearrangement and Cyclization Reactions

Ming De Wang and Howard Alper*

Contribution from the Department of Chemistry, Ottawa-Carleton Chemistry Institute, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5. *Received December 26, 1991*

Abstract: Carbonylation of pyrrolidines, catalyzed by cobalt carbonyl, results in the formation of piperidinones. The reaction is regiospecific in most cases, and the yield of product is increased when ruthenium carbonyl is present as a second catalyst. The dual catalytic system $[Co_2(CO)_8/Ru_3(CO)_{12}]$ is useful for the novel rearrangement of heterocyclic nitrogen ketones $[\overline{(CH_2)_n}NCH_2COR$, n = 4-7] to lactams in 72-93% yields. An unusual metal catalyzed cyclization reaction of 2,6-dimethylpiperidinyl ketones afforded 5,6,7,8-tetrahydroindolizines in 86-94% yields.

Carbonylation based methodologies for the construction of lactams have attracted considerable interest in recent years,[1,2] Both stoichiometric and catalytic processes have been developed including, among others, the photochemical reaction of carbene chromium complexes with imines to give β-lactams in good yields[3] and the cyclization of *N*-alkyl-2-bromophenethylamines with carbon monoxide to form tetrahydroisoquinol-1-ones, a reaction catalyzed by palladium acetate in the presence of triphenylphosphine.[4]

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