Hz, 1-H), 2.30 (dd, J = 3.8, 17.2 Hz, 1-H), 1.88 (m, 1-H), 1.03 (d, J = 6.8 Hz, 3-H), 0.99 (d, J = 6.8 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ 173.47, 166.96, 138.40, 128.33, 127.79, 127.60, 90.04, 84.64, 77.24, 75.00, 55.98, 29.91, 28.01, 19.40, 18.57. Capillary GC analysis indicated a purity of 99%.

6-[1-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (18a, *threo*): ^{1}H NMR ($CDCl_3$) δ 5.14 (d, J = 2.0 Hz, 1-H), 4.30 (ddd, J = 3.8, 5.8, 12.7 Hz, 1-H), 3.75 (s, 3-H), 3.63 (m, J = 3.8, 5.8 Hz, 1-H), 2.55 (ddd, J = 2.0, 12.7, 17 Hz, 1-H), 2.23 (dd, J = 3.8, 17 Hz, 1-H), 1.82 (m, 1-H), 1.02 (d, J = 6.8 Hz, 3-H), 0.92 (s, 9-H), 0.89 (d (partial overlap), 3-H), 0.14 (s, 3-H), 0.1 (s, 3-H); ^{13}C NMR ($CDCl_3$) δ 172.70, 139.66, 90.48, 78.51, 77.54, 68.82, 56.03, 29.96, 29.32, 26.11, 16.53, −3.76. Capillary GC analysis indicated a purity of 98%.

6-[1-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (18b, *erythro*): mass calcd for $C_{16}H_{30}O_4Si$ (M + 1), 315.1991; exact mass (CI, M + 1) 315.1995; MS (NH_3/CI) 257, 157, 139, 74, 58; ^{1}H NMR ($CDCl_3$) δ 5.12 (d, J = 1.6 Hz, 1-H), 4.41 (dt, J = 3.4, 12.2 Hz, 1-H), 3.75 (s, 3-H), 3.67 (dd, J = 3.4, 6.8 Hz, 1-H), 2.81 (ddd, J = 1.6, 12.2, 17 Hz, 1-H), 2.20 (dd, J = 3.4, 17 Hz, 1-H), 1.72 (m, 1-H), 0.97 (d, J = 6.8 Hz, 3-H), 0.91 (d (partial overlap), 3-H), 0.90 (s, 9-H), 0.11 (s, 6-H); ^{13}C NMR ($CDCl_3$) δ 178.8, 173.3, 90.01, 77.85, 77.24, 55.96, 31.27, 27.44, 26.10, 19.17, 18.99, −3.69, −4.3. Capillary GC analysis indicated a purity of 97%.

Methyl 6-(benzyloxy)-3-methoxy-7-methyl-5-hydroxy-2-octenoate (20): ^{1}H NMR ($CDCl_3$) δ 7.30–7.50 (m, 5-H), 5.14 (s, 1-H), 4.69 (s, 2-H), 4.05 (m, 1-H), 3.68 (s, 3-H), 3.66 (s, 3-H), 3.25 (dd, J = 9.5, 13.5 Hz, 1-H), 3.09 (dd, J = 3.4, 6.35 Hz, 1-H), 2.83 (s, 1-H), 2.79 (dd, J = 3.9, 9.5 Hz, 1-H), 2.05 (m, 1-H), 1.02 (d, 6-H). Capillary GC indicated a purity of 98%.

6-[1-(Benzyloxy)-2,2-dimethylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (19a, *threo*): mass calcd for $C_{18}H_{24}O_4$ (M + 1), 305.1753; exact mass (CI, M + 1) 305.1745; MS (NH_3/CI) 177, 157, 127, 91, 83, 49; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5-H), 5.10 (d, J = 1.47 Hz, 1-H), 4.61–4.71 (m, 3-H), 3.69 (s, 3-H), 3.09 (d, J = 2.44 Hz, 1-H), 2.83 (ddd, J = 1.46, 11.7, 16.6 Hz, 1-H), 2.23 (dd, J = 3.9, 16.6 Hz, 1-H), 1.11 (s, 9-H); ^{13}C NMR ($CDCl_3$) δ 172.8, 167, 138.3, 128.5, 128.3, 127.6, 127.3, 90.2, 87.7, 76.1, 55.9, 36.4, 31.1, 27.5. Capillary GC analysis indicated a purity of 100%.

6-[1-(Benzyloxy)-2,2-dimethylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (19b, *erythro*): ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5-H), 5.14 (d, J = 1.46 Hz, 1-H), 4.88 (d, J = 11.7 Hz, 1-H), 4.62 (d (overlap), J = 11.7 Hz, 1-H), 4.61–4.63 (ddd (overlap), J = 1.95, 3.91, 12.2 Hz, 1-H), 3.74 (s, 3-H), 3.53 (d, J = 1.96 Hz, 1-H), 2.95 (ddd, J = 1.47, 12.21, 17.6 Hz, 1-H), 2.30 (dd, J = 3.91, 17.6 Hz, 1-H), 1.01 (s, 9-H); ^{13}C NMR ($CDCl_3$) δ 173.9, 138.54, 128.3, 127.4, 89.89, 87.58, 75.30, 56.02, 35.16, 29.20, 26.95. Capillary GC analysis indicated a purity of 100%.

Acknowledgment. Financial support was provided by the University of California, Riverside Chancellor's Patent Fund, the Committe on Research, and the National Institutes of Health (NIH), grant GM24517. The assistance of Rich Kondrat in providing mass spectra and Jim O'Brien in preparation of allylic alcohols is gratefully acknowledged.

Supplementary Material Available: NMR (^{1}H and ^{13}C) spectral data for compounds 4a,[26] 4b, 4c,[26,29], 4d,[26] 5a–d, 8a,[5e] 8b,[5b,8] 11–13, and 17–19 (11 pages). Ordering information is given on any current masthead page.

Asymmetric Diels–Alder Reactions with γ-Functionalized α,β-Unsaturated Chiral *N*-Acyloxazolidinones: Synthesis of (+)-S-145

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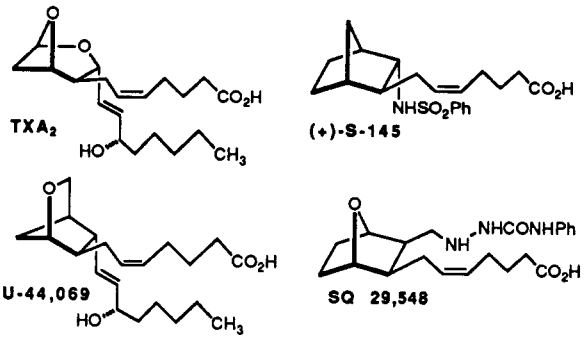
An extension of the asymmetric Diels–Alder cycloaddition with chiral γ-substituted, α,β-unsaturated imides is described. The application of these results to the synthesis of the potent TxA_2 receptor antagonist (+)-S-145 was successfully achieved in a practical manner.

Thromboxane A2 (TxA_2) receptor antagonists are an important class of pharmacological tools and are being studied clinically for the treatment of diseases such as asthma, angina pectoris, thrombosis, and other circulatory disorders.[1] A number of reports that discuss TxA_2 receptor antagonists have appeared recently.[1,2] In most cases, replacement of one or both of the ring substituted oxygen atoms of TxA_2, while maintaining the bicyclic steric nature of the ring system, has resulted in the discovery of very potent compounds with higher stability than TxA_2 itself (below). Moreover, modification of the α and ω side chains has also been shown to modulate the potency and intrinsic efficacy of these compounds at the TxA_2 receptor. The norbornyl nucleus has served as a pivotal framework on which to append various α and/or ω moieties, and S-145 is a potent norbornyl-derived TxA_2 receptor antagonist.[1a] We desired access to an optically active, substituted norbornyl ring which would allow flexibility for functionalization of the side chains in order to obtain the desired biological activity. As part of a collaboration with chemists at Shionogi and Company, we were interested in developing synthetic methodology for the preparation of highly substituted, optically active norbornane derivatives.



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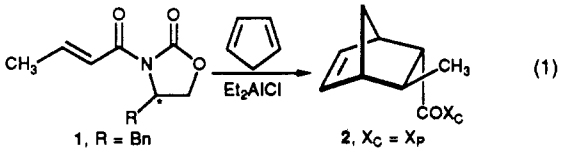
An attractive entry into the optically active norbornyl series was obviously the enantioselective Diels–Alder cycloaddition reaction, a subject which has recently received much attention.[3] Lewis acids have been used to increase dienophile reactivity, thereby allowing the cycloaddition to occur at lower temperatures with higher endo selectivity.[4] Dienophiles containing a chiral auxiliary form complexes with a variety of Lewis acids and undergo Diels–Alder cycloadditions with very high asymmetric induction and chemical yields.[5] Alternatively, Lewis acids with chiral ligands have been effective mediators of cycloaddition as well, both as stoichiometric reagents[6] and as catalysts.[7] We were especially enthusiastic about the Evans version of the asymmetric Diels–Alder reaction (eq 1).[8] A chiral oxazolidinone, derived from an amino acid,



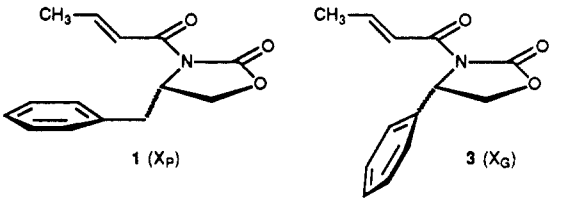
(1)

was coupled with crotonyl chloride to afford an optically active imide dienophile. The dienophile was then allowed to react with a variety of dienes and Et_2AlCl at low temperature to afford adducts with high diastereoselectivities (>90% de) and chemical yields (85%). The oxazolidinones were later removed under a variety of conditions.[8,9] We were particularly interested in extending these results to terminus-substituted crotyl dienophiles and their reaction with cyclopentadiene, ultimately followed by elaboration to the potent TxA_2 receptor antagonist (+)-S-145 (above).

Results and Discussion

At the outset, we wanted to determine the most desirable chiral oxazolidinone auxiliary to employ in our studies. Several chiral oxazolidinones (X_C) have been used; for example, the (*S*)-valinol-derived (X_V), (4*R*,5*S*)-norephedrine-derived (X_N), (*S*)-phenylalaninol-derived (X_P), cyclohexyl-derived (X_{PPG}), and the cyclohexylmethyl-derived (X_{PPA}) were compared.[8] That comparison concluded that the (*S*)-phenylalaninol-derived (X_P) oxazolidinone was superior to the other oxazolidinones (X_V, X_N) as an auxiliary in the diastereoselective cycloaddition reaction, and furthermore, X_P offered a higher degree of crystallinity and possessed a chromophore for TLC/HPLC analysis which does not interfere with the ^1H NMR upfield resonances. The (*S*)-phenylalaninol-derived (X_P) oxazolidinone was commercially available or readily prepared in two steps on a mole scale.[9]

However, we had ready access to the (*S*)-phenylglycinol-derived (X_G) oxazolidinone from related work, and although it has not been reported for use as an auxiliary in the cycloaddition with cyclopentadiene, we needed to evaluate its utility. The X_G oxazolidinone was coupled with crotonyl chloride to afford the dienophile **3** in 93% isolated yield. The dienophile **3** was then reacted with Et_2AlCl in CH_2Cl_2 at −78 °C, followed by the addition of freshly distilled cyclopentadiene. Alternatively, the imide–cyclopentadiene admixture could be treated with Et_2AlCl at −78 °C as well. After 30 minutes at −78 °C, workup provided identical results irrespective of the order of addition. The X_G-based dienophile **3** gave very high endo selectivity, but surprisingly, gave no asymmetric induction with cyclopentadiene as the diene component. The 1:1 mixture of diastereomeric adducts **4** was treated with LiOOH in aqueous THF[10] to cleave the chiral oxazolidinone. This yielded a racemic mixture of the acid, which displayed a homogeneous NMR spectrum, as expected, since the endo and exo isomers could be easily distinguished by ^1H NMR spectroscopy. Evans and coworkers have advanced the notion of "π-solvation" in the transition state to rationalize similar stereochemical results (below).[8,11] On the basis of these results and the X_C comparison described above, the X_P auxiliary was employed in all subsequent cycloadditions outlined below.



We next turned our attention to terminus-substituted crotyl imide dienophiles. It was not clear at the outset what effect a terminal heteroatom or halogen would have on the cycloaddition, both with respect to competing chelation, elimination, or reaction with the Lewis acid itself. In most cases, the acid or ester was commercially available. We employed two complementary protocols for the construction of the α,β-unsaturated imides. In the first procedure, the α,β-unsaturated acid was converted to the acid chloride and purified by vacuum distillation, followed by reaction with the lithium salt of the oxazolidinone (X_PLi) to obtain the imide. For cases where the α,β-unsaturated acid chloride formation proved to be unachievable (due to polymerization/decomposition), the acid was converted to its pivaloyl mixed anhydride in situ, followed by reaction with X_PLi. This procedure offered the advantage of in situ activation, eliminating one isolation step from the scheme. The imides could be purified by crystallization or chromatography. Table I outlines the imides that were prepared for this study.

The Diels–Alder cycloadditions were conducted in CH_2Cl_2 at −78 °C with Et_2AlCl (1.4 molar equiv) and

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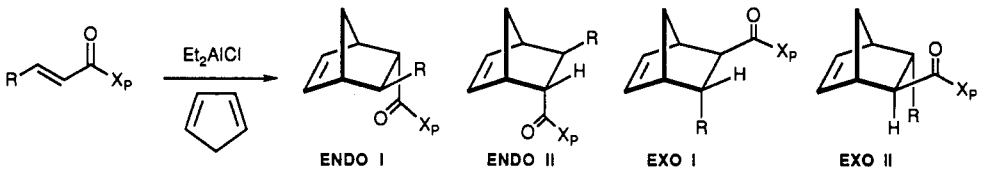
Table I. Product Distribution from the Asymmetric Diels–Alder Reactions of γ-Substituted α,β-Unsaturated Imides with Cyclopentadiene



entry	dienophile	method[a]	adduct	method[b]	% yield[c]	temp, °C	$\Sigma_{endo}/\Sigma_{exo}$[d]	I/II endo ds
A	1, R = CH_3	Cl	2	E_1 or C_1	83	−100	55:1	97:3
B	3, R = CH_3 (X_C)	Cl	4	E_1 or C_1	93	−78	–	1:1
C	5, R = $CH_2CH_2CH_3$	Pv	6	E_1 or C_1	95	−78	46:1	96:4
D	7, R = $CH{=}CHCH_3$ (t)	Cl	8	C_1	75	−45	45:1	99:1
E	9, R = CH_2CH_2OBn	Pv	10	E_1	92	−78	36:1	97:3
F	11, R = CH_2OBn	Pv	12	E_1	86	−78	35:1	98:2
G	13, R = CH_2Br	NBS	14	C_1	91	−78	29:1	99:1
H	15, R = 2-furanyl	Pv	16	E_1	81	−40	37:1	95:5
I	17, R = CO_2Et	Cl	18	C_1	89	−78	6.4:1	95:5
J	19, R = COX_P	Cl	20	C_1	83	−78	1:0	99:1
K	19, R = COX_P	Cl	20	NE	99	24	1:0	2:1

[a] Method for preparation of the α,β-unsaturated imide (see Experimental Section). [b] Mode of addition in Diels–Alder cycloaddition (NE = no Et_2AlCl added). [c] Yield of isolated material with indicated diastereomeric purity. [d] Ratios determined by HPLC.

freshly distilled cyclopentadiene (3–6 equiv) for 2 h under N_2. The order of addition was critical in some cases due to the nature of the dienophile: Et_2AlCl first, cyclopentadiene second (E_1); or cyclopentadiene first, Et_2AlCl second (C_1). For example, with very electron deficient dienophiles (e.g., R = CO_2Et (17), COX_P (19)), the Et_2AlCl formed an adduct with the olefin in the absence of the diene partner. Therefore, cyclopentadiene needed to be present prior to the addition of the Lewis acid. However, for more electron rich dienophiles, the cycloaddition was extremely slow at −78 °C and required warming to −45 °C for complete reaction (e.g., R = $CH{=}CHCH_3$ (7), furan (15), Ph[8]). The other examples were insensitive to the order of addition, and the results are summarized in Table I. The diastereoselectivity was determined by HPLC with comparison of authentic samples of the four possible diastereomers, prepared by nonselective cycloaddition of the α,β-unsaturated acid with ultimate conversion to the imide via the mixed anhydride method. The observed endo diastereoselectivities were in complete agreement with the literature precedent,[8] typically in excess of 97:3. The absolute stereochemical assignment relies in part upon the analysis of Evans and co-workers.[8] Nonetheless, this assignment was confirmed by the conversion of adduct 10 to the TxA_2 receptor antagonist (+)-S-145, a compound of known configuration (vide infra).

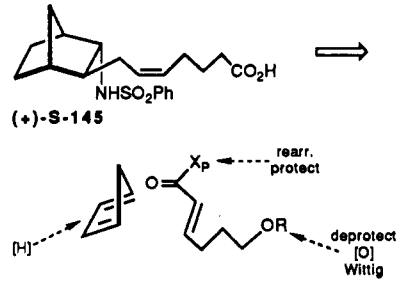
For practical considerations, it was interesting to determine the relationship between diastereoselectivity and temperature, especially in terms of scale-up latitude. Thus, the temperature dependence of the Et_2AlCl-mediated reaction of imide 9 with cyclopentadiene was investigated. As expected, lower temperatures gave higher selectivity, but solubility became an issue at temperatures below −85 °C, although addition of the Lewis acid caused dissolution. The endo diastereoselectivity was less affected by temperatures above −70 °C, as compared to the endo/exo selectivity. These data are presented in Table II. The reactive nature of α,β-unsaturated imides has previously been noted,[8] and this reactivity was especially enhanced with Lewis acids. It was interesting to note that the bisimide 19 underwent rapid cycloaddition with cyclopentadiene at room temperature without Et_2AlCl (Table I, entry K).

The fact that this Lewis acid mediated cycloaddition could be accomplished with potentially sensitive dienophiles, i.e. those bearing halogens or heteroatoms, indicated the mild nature of these conditions. The only side products observed were those resulting from conjugate addition of the Lewis acid to the α,β-unsaturated imide,[12] as in the case where R = CO_2Et (17), COX_P (19). This problem could be overcome by recognizing the importance of the order of addition. Even reactive olefins such as the bromocrotonate imide 13, which was unstable to prolonged storage at room temperature, were well-behaved in the cycloaddition described above.

Table II. Temperature Effect on Selectivity in Asymmetric Diels–Alder Cycloaddition for Imide 9 → Adduct 10

temp, °C	end ds	$\Sigma_{endo}/\Sigma_{exo}$
0	92.0:8.0	8:1
−45	95.0:5.0	17:1
−70	96.0:4.0	28.1
−85	96.5:3.5	36:1
−100	97.0:3.0	65:1

Application to (+)-S-145. The retrosynthetic analysis of (+)-S-145 immediately suggested a Wittig transform[1,13] to the requisite aldehyde, easily derived from a protected alcohol moiety. The C-1 carbonyl to nitrogen transposition could be envisioned through a Curtius or Hoffman type rearrangement. Standard protection–deprotection and oxidation–reduction operations at various points in the scheme would result in a very facile assembly of the title compound (below). In actual practice, the synthesis used very inexpensive and commercially available starting materials and is described below.



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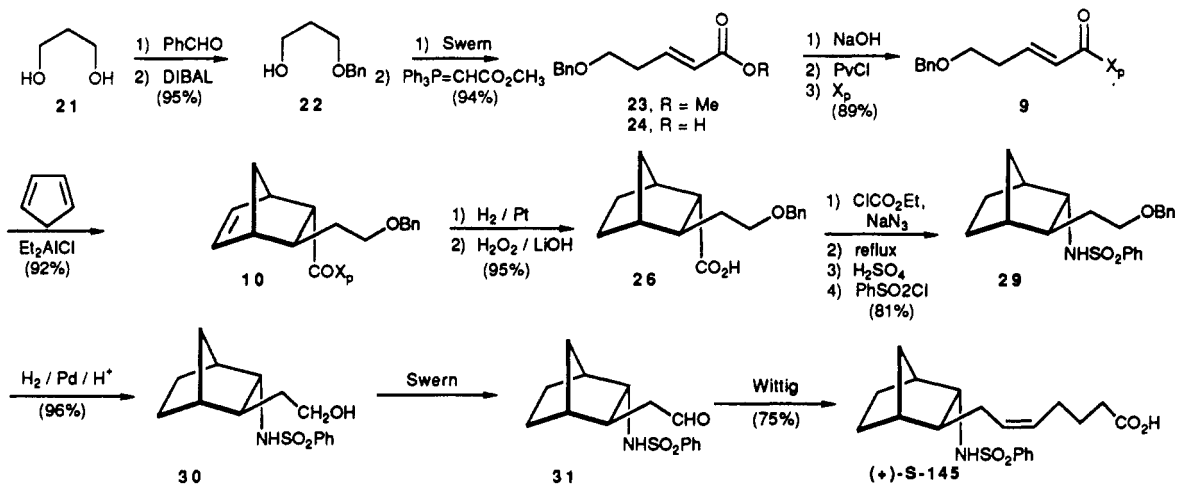
Scheme I



1,3-Propanediol (21) was monobenzylated by a one-pot, two-step sequence as follows. Benzylidene acetal formation occurred in toluene with azeotropic removal of water (Scheme I). The cooled solution of the acetal was then reduced with DIBAL-H overnight at room temperature. The excess reducing agent was quenched with methanol/water, and the aluminum salts which precipitated were filtered. Concentration of the filtrate allowed very simple access to molar quantities of 3-(benzyloxy)-1-propanol (22).[14] The Ireland version[15] of the Swern–Wittig reaction sequence was employed next. Namely, usual Swern oxidation ($DMSO/(COCl)_2/Et_3N$) generated the β-alkoxy aldehyde, which, without isolation, was reacted directly with the methyl (triphenylphosphoranylidene)acetate[16] (−78 °C to room temperature) in CH_2Cl_2. After aqueous workup, trituration with hexanes and filtration removed the triphenylphosphine oxide from the desired α,β-unsaturated ester **23**. The E/Z ratio was determined to be 98:2, although the geometry of the olefin does not affect the stereochemistry of the Diels–Alder reaction.[17] Hydrolysis of the ester **23** with NaOH in aqueous THF provided the acid **24**. This strategy allowed a very rapid assembly of the requisite dienophile chain, with an 88% overall yield from 1,3-propanediol (Scheme I). This scheme was also applied to the synthesis of **11**.

The acid **24** was then coupled to the oxazolidinone X_P through the intermediacy of the pivaloyl mixed anhydride in 88%. The mixed anhydride protocol was found to be superior to acid chloride procedure in the case of **24**. Diels–Alder cycloaddition as described previously proceeded smoothly at −78 °C. After 2 h, careful addition of the reaction mixture to ice-cold 1 N HCl allowed a very controlled evolution of ethane, and the adduct **10** was isolated by extraction into CH_2Cl_2. Although the diastereoselectivity for this reaction was high, one means for improvement of the purity of these isomeric adducts might have been recrystallization, since they are diastereomeric. We were unable to induce the Diels–Alder adduct **10** to crystallize and therefore could not take advantage of this approach. Direct hydrolysis of the imide **10** with LiOOH[10] was accompanied by a side reaction at the olefinic center, in addition to reaction at the desired imide carbonyl. Although LiOOH has been previously used in the hydrolysis of imide substrates containing unsaturation,[10] the bicyclo[2.2.1]heptene nucleus has a highly reactive, strained double bond moiety. The double bond was therefore reduced over catalytic PtO_2 under an atmosphere of hydrogen to yield the saturated bicycle **25** (Scheme I). Once again, the lack of crystallinity of this compound precluded improvement of the optical purity at this point.

Cleavage of the auxiliary proceeded smoothly with the saturated substrate **25**, and the acid **26** could be purified by extraction into aqueous base with organic extraction for retrieval of the auxiliary. Adjustment of the pH and extractive isolation gave the acid **26** in high yield (88%). Crystallization of the auxiliary from the original organic extract afforded an 85% recovery, easily accomplished on a large scale (>100 g). We have established that the optical purity of this recovered oxazolidinone (X_P) was unchanged, and the auxiliary was recycled successfully. Thus, the chiral oxazolidinone was appended to the dienophile **24** in a single operation, the Diels–Alder reaction was completed, and the auxiliary was removed and recycled.

Once again, the mixed anhydride technology was employed for the activation of an acid moiety. Thus, reaction of the acid **26** with ethyl chloroformate and Et_3N in wet acetone, followed by the addition of aqueous sodium azide,[18] afforded the acyl azide. After aqueous workup and extraction with toluene, the acetone was evaporated and the resulting toluene solution was brought to reflux for 1 h. The toluene was removed at reduced pressure; the residue was dissolved in THF and cooled to 0 °C. The addition of concentrated sulfuric acid[19] gave a very smooth evolution of CO_2. Hydrolysis of the intermediate isocyanate **27** with aqueous HCl or $TsOH\cdot H_2O$, however, was very slow and usually resulted in formation of high levels of the urea. The primary amine **28**, isolated by neutralization and extraction, was converted directly to the benzenesulfonamide **29** with $PhSO_2Cl$ (Scheme I). The acid **26** was converted to the sulfonamide **29**, without isolation of any intermediate, in 80% overall yield.

Furthermore, the intermediate isocyanate **27** could also be treated with benzyl alcohol to afford the CBz-protected product **32** (below). This was useful for later modification

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(17) It has previously been demonstrated that the *Z* olefin undergoes rapid isomerization to the *E* olefin in the presence of Et_2AlCl, faster than cycloaddition with cyclopentadiene. See ref 8.
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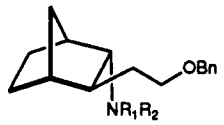
of the substituent at nitrogen. The primary amine **28**, obtained from hydrolysis of the isocyanate **27**, was also converted to the corresponding Mosher's amide[20] **33**, although analysis of the diastereomers by chromatographic or spectroscopic methods was not possible. An alternative to the acyl azide procedure above was the $(PhO)_2PON_3$ (DPPA) method of Yamada.[21] Reaction of the acid **36** with DPPA in toluene, followed by benzyl alcohol at reflux, afforded the CBz amide **32** in moderate yields.



27, R_1,R_2 = C=O
28, R_1,R_2 = H
32, R_1 = H, R_2 = CO_2Bn
33, R_1 = H, R_2 = $COC(CF_3)(OMe)Ph$

The sulfonamide **29** was then debenzylated by catalytic reduction over Pd/C in ethanol solution containing a catalytic amount of HCl.[22] The same reduction in the absence of HCl was extremely slow and could not be driven to completion even with large loads of Pd/C. Nevertheless, the addition of aqueous HCl caused a rapid debenzylation. The material thus obtained could be crystallized from toluene to afford the alcohol **30** in 96% yield (Scheme I). At this point, formation of the Mosher's ester of the crude alcohol confirmed the enantio- and diastereomeric purity of the product from the Diels–Alder step. Simple recrystallization of the alcohol **30**, however, resulted in a slight enantiomeric enrichment,[23] as well as overall purification (>98% ee and de).

Swern oxidation of the alcohol provided the aldehyde **31**, which could be isolated and recrystallized or subjected directly to the Wittig reaction according to the procedure described by Narisada et al.[1,13] Thus, formation of the dianion of the ylide **34**, derived from (4-carboxybutyl)-triphenylphosphonium bromide in THF at room temperature, followed by addition of the aldehyde at −20 °C (2 h) then 23 °C (1.5 h), afforded (+)-S-145 in 75–80% yield (two steps, Scheme I). The *E*/*Z* ratio of this cis-olefination was 8:92, which compared favorably to that reported by Narisada et al.,[1a] and the undesired *E* isomer was easily removed by chromatography. Recrystallization from a mixture of toluene/hexanes afforded (+)-S-145 in 40% overall yield, containing <1% (−)-S-145 and <1% of the corresponding exo-isomer (HPLC).

Conclusions

The asymmetric version of the Diels–Alder cycloaddition, employing a chiral oxazolidinone auxiliary and promoted by a Lewis acid, was extended to functionalized dienophiles. The auxiliary was easily installed onto the dienophile, easily removed in high yield under mild conditions by a nondestructive method, and recovered in a very practical manner. The recovered oxazolidinone auxiliary was furthermore recycled in the Diels–Alder reaction. A very high level of asymmetric induction was obtained with the phenylalaninol-derived oxazolidinone (X_P) from the Diels–Alder cycloaddition with >98% purity. The utility of the technology was highlighted by an efficient synthesis of (+)-S-145, a potent TxA_2 receptor antagonist. The asymmetric Diels–Alder reaction may be extended to a wide variety of *E*-α,β-unsaturated imides to allow a versatile access to optically active norbornyl derivatives.

Experimental Section

General. ^1H and ^{13}C spectra were obtained at 300 and 75.5 MHz, respectively. Melting points were determined on a Reichert-Jung hot stage microscope and are uncorrected. Diethylaluminum chloride was obtained from Aldrich. Solvents were purified according to standard procedures,[24] and dicyclopentadiene was depolymerized according to the method of Moffett.[25] Analytical HPLC was performed on a liquid chromatograph equipped with a detector. The specific conditions are reported for each assay below.

General Procedure for α,β-Unsaturated Imide Preparation. The imides were prepared according to the procedure noted in Table I. Cl: Cl refers to formation of the imide from the appropriate acid chloride according to the general protocol described by Evans.[8] Pv: Pv refers to formation of the imide via the pivaloyl mixed anhydride as described for imide **9**, below. NBS: The bromocrotonimide **13** was prepared from crotonimide **1**[8] as described below.

General Procedure for Diels–Alder Cycloaddition. The α,β-unsaturated imide was dissolved in CH_2Cl_2 (ca. 0.5 M) and cooled to −78 °C under N_2. The order of addition was noted in Table I, and corresponds to the two different protocols. (1) C_1: Freshly distilled cyclopentadiene (4–6 equiv) was then added to the reaction mixture, followed by the dropwise addition of Et_2AlCl (1.4 equiv) diluted with 3 volumes CH_2Cl_2. (2) E_1: Et_2AlCl (1.4 equiv) diluted with 3 volumes CH_2Cl_2 was added dropwise, and to the resulting yellow solution was then added cyclopentadiene (4–6 equiv). In both procedures, the reaction mixture was allowed to stir at −78 °C under N_2 for 2 h and then transferred via cannula into a stirred solution of 1 N HCl at 0 °C. The layers were separated, and the organic phase was washed successively with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, and brine and dried (Na_2SO_4). The filtrate was concentrated to dryness and passed through a plug of SiO_2 to remove polymerized cyclopentadiene.

(4*S*)-3-((*E*)-2′-Butenoyl)-4-phenyl-2-oxazolidinone (3): 93%; mp 82–83 °C; R_f 0.69 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, *m*/*e* 231 (M^+); IR ($CHCl_3$) 2896, 1780, 1602, 1385 cm^{-1}; NMR ($CDCl_3$) δ 1.93 (dd, 3 H, *J* = 1.3, 6.8 Hz), 4.27 (dd, 1 H, *J* = 3.9, 8.8 Hz), 4.70 (t, 1 H, *J* = 8.8 Hz), 5.48 (dd, 1 H, *J* = 3.9, 8.8 Hz), 7.08 (dq, 1 H, *J* = 6.8, 15.4 Hz), 7.24–7.40 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 18.4, 57.6, 69.8, 121.6, 125.8, 128.5, 129.0, 139.1, 147.1, 153.6, 164.3; UV (EtOH) λ_{max} (ε) 226 (10500); $[\alpha]_{589}$ +154.3° (*c* 1.01, MeOH).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.78; H, 5.73; N, 6.02.

(4*S*)-3-((*E*)-2′-Hexenoyl)-4-(phenylmethyl)-2-oxazolidinone (5): 80%; R_f 0.80 (silica gel, 1:1 hexanes–EtOAc); mass spectrum, *m*/*e* 273 (M^+); IR ($CHCl_3$) 3020, 1778, 1682, 1635, 1356 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (t, 3 H, *J* = 7.4 Hz), 1.54 (m, 2 H), 2.28 (m, 2 H), 2.77 (dd, 1 H, *J* = 9.6, 13.4 Hz), 3.32 (dd, 1 H, *J* = 3.2, 13.4 Hz), 4.19 (m, 2 H), 4.74 (m, 1 H), 7.21–7.38 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 13.7, 21.3, 34.7, 37.9, 55.3, 66.1, 120.5, 127.3, 128.9, 129.4, 135.4, 151.7, 153.4, 165.1; UV (EtOH) λ_{max} (ε) 229 (17900), 217 (15500); $[\alpha]_{589}$ −13.3° (*c* 1.02, MeOH).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.06; H, 6.94; N, 5.12.

(4*S*)-3-((*E*,*E*)-2′,4′-Hexadienoyl)-4-(phenylmethyl)-2-oxazolidinone (7): 93%; R_f 0.64 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, *m*/*e* 272 (M + 1); IR ($CHCl_3$) 1776, 1678, 1635, 1602, 1380, 1354 cm^{-1}; NMR ($CDCl_3$) δ 1.89 (d, 3 H, *J* = 6.0 Hz), 2.81 (dd, 1 H, *J* = 9.6, 13.8 Hz), 3.33 (dd, 1 H, *J* = 3.0, 13.8 Hz), 4.18 (m, 2 H), 4.74 (m, 1 H), 6.19–6.41 (m, 2 H), 7.14–7.36 (m, 6 H), 7.49 (dd, 1 H, *J* = 10.2, 15.6 Hz); ^{13}C NMR ($CDCl_3$) δ 18.8,

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37.9, 55.3, 66.0, 117.9, 127.2, 128.9, 129.4, 130.4, 135.4, 141.2, 146.9, 153.4, 165.5; UV (EtOH) λ_{max} (ϵ) 278 (25 300), 206 (11 200); $[\alpha]_{589}$ +205.6° (*c* 1.00, MeOH).

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.84; H, 6.06; N, 5.01.

(4*S*)-3-((*E*)-4'-(Benzyloxy)-2'-butenoyl)-4-(phenylmethyl)-2-oxazolidinone (11): 87%; R_f 0.70 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, *m/e* 351 (M^+); IR ($CHCl_3$) 1780, 1685, 1354 cm^{-1}; NMR ($CDCl_3$) δ 2.81 (dd, 1 H, *J* = 3.2, 13.4 Hz), 3.34 (dd, 1 H, *J* = 9.6, 13.4 Hz), 4.20 (m, 2 H), 4.26 (dd, 2 H, *J* = 1.8, 4.4 Hz), 4.61 (s, 2 H), 4.74 (m, 1 H), 7.17–7.38 (m, 11 H), 7.57 (dt, 1 H, *J* = 1.8, 15.5 Hz); ^{13}C NMR ($CDCl_3$) δ 37.9, 55.3, 66.2, 69.0, 72.8, 120.6, 127.4, 127.8, 127.9, 128.5, 129.0, 129.5, 135.3, 137.7, 146.4, 153.3, 164.7; UV (EtOH) λ_{max} (ϵ) 226 (15 000), 208 (22 600); $[\alpha]_{589}$ +0.52° (*c* 1.01, MeOH).

Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.49; H, 6.11; N, 4.20.

(4*S*)-3-((*E*)-4'-Bromo-2'-butenoyl)-4-(phenylmethyl)-2-oxazolidinone (13). The imide 1 (1.10 g, 4.5 mmol) was dissolved in CCl_4 (20 mL), and NBS (958 mg, 5.4 mmol) was added in one portion. The solution was brought to reflux under N_2, and a solution of 2,2'-azobis[2-methylpropionitrile] (736 mg, 4.5 mmol) in CCl_4 (10 mL) was added via syringe pump over 1 h. When the addition was complete, the reaction mixture was cooled to room temperature, washed successively with aqueous $NaHCO_3$, H_2O, and brine, and dried (Na_2SO_4). The filtrate was concentrated to dryness and chromatographed over SiO_2 with hexanes–EtOAc (3:1); 57%; R_f 0.64 (silica gel, 1:1 hexanes–EtOAc); mass spectrum, *m/e* 323/325 (M^+); IR ($CHCl_3$) 1780, 1686, 1637, 1357 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (dd, 1 H, *J* = 9.5, 13.4 Hz), 3.34 (dd, 1 H, *J* = 2.9, 13.4 Hz), 4.10 (dd, 2 H, *J* = 1.0, 7.4 Hz), 4.21 (m, 2 H), 4.73 (m, 1 H), 7.18–7.49 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.4, 37.7, 55.2, 66.2, 123.2, 127.3, 128.9, 129.4, 135.1, 143.2, 153.2, 163.9; UV (EtOH) λ_{max} (ϵ) 229 (15 400), 211 (15 900); $[\alpha]_{589}$ +125.0° (*c* 1.01, MeOH).

Anal. Calcd for $C_{14}H_{14}NO_5Br$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.58; H, 4.38; N, 4.27.

(4*S*)-3-((*E*)-3'-(2-Furanyl)-2'-propenoyl)-4-(phenylmethyl)-2-oxazolidinone (15): 69%; R_f 0.63 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, *m/e* 297 (M^+); IR ($CHCl_3$) 1777, 1675, 1618, 1556, 1353 cm^{-1}; NMR ($CDCl_3$) δ 2.84 (dd, 1 H, *J* = 3.2, 13.4 Hz), 3.36 (dd, 1 H, *J* = 9.5, 13.4 Hz), 4.21 (m, 2 H), 4.81 (m, 1 H), 6.50 (dd, 1 H, *J* = 1.8, 3.4 Hz), 6.72 (d, 1 H, *J* = 3.4 Hz), 7.22–7.35 (m, 5 H), 7.53 (m, 1 H), 7.66 (d, 1 H, *J* = 15.4 Hz), 7.76 (d, 1 H, *J* = 15.4 Hz); ^{13}C NMR ($CDCl_3$) δ 37.9, 55.4, 66.1, 112.5, 114.6, 116.1, 127.3, 129.0, 129.5, 132.3, 135.4, 145.3, 151.4, 153.4, 165.1; UV (EtOH) λ_{max} (ϵ) 321 (26 500), 237 (4960); $[\alpha]_{589}$ +146.6 (*c* 1.00, MeOH).

Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.52; H, 5.20; N, 4.74.

(4*S*)-3-((*E*)-3'-(Ethoxycarbonyl)-2'-propenoyl)-4-(phenylmethyl)-2-oxazolidinone (17): 67%; R_f 0.55 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, *m/e* 303 (M^+); IR ($CHCl_3$) 1785, 1723, 1686, 1633, 1357 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (t, 3 H, *J* = 7.1 Hz), 2.83 (dd, 1 H, *J* = 9.4, 13.4 Hz), 3.33 (dd, 1 H, *J* = 3.2, 13.4 Hz), 4.27 (m, 4 H), 4.75 (m, 1 H), 6.98 (d, 1 H, *J* = 15.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 37.6, 55.3, 61.4, 66.5, 127.5, 129.1, 129.4, 132.3, 134.4, 134.9, 153.1, 163.8, 164.9; UV (EtOH) λ_{max} (ϵ) 211 (20 400); $[\alpha]_{589}$ +133.0° (*c* 1.00, MeOH).

Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.15; H, 5.81; N, 4.53.

(4*S*)-3-(4'-Oxo-4'-((4''*S*)-2''-oxo-4''-(phenylmethyl)-3''-oxazolidinyl)-2'(*E*)-butenoyl)-4-(phenylmethyl)-2-oxazolidinone (19): 88%; R_f 0.76 (silica gel, 9:1 CH_2Cl_2–EtOAc); mass spectrum, *m/e* 435 (M + 1); IR ($CHCl_3$) 1785, 1680, 1355 cm^{-1}; NMR ($CDCl_3$) δ 2.85 (dd, 2 H, *J* = 9.6, 13.4 Hz), 3.39 (dd, 2 H, *J* = 2.9, 13.4 Hz), 4.26 (m, 4 H), 4.77 (m, 2 H), 7.16–7.38 (m, 10 H), 8.27 (s, 2 H); ^{13}C NMR (DMSO) δ 36.5, 54.6, 66.6, 126.9, 128.6, 129.4, 132.4, 135.4, 153.2, 163.2; UV (EtOH) λ_{max} (ϵ) 234 (16 200), 208 (19 600); $[\alpha]_{589}$ +40.2° (*c* 0.99, MeOH).

Anal. Calcd for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.08; H, 5.00; N, 6.49.

Adducts, R = CH_3 (4, X_G): 93%; R_f 0.80 (silica gel, 1:1 hexanes–EtOAc); mass spectrum, *m/e* 297 (M^+); IR ($CHCl_3$) 2980, 1779, 1693, 1390, 1320, 1198 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (m, 6 H), 1.24 (m, 2 H), 1.71 (m, 2 H), 1.98 (m, 2 H), 2.48 (m, 2 H), 3.30 (m, 2 H), 3.60 (m, 2 H), 4.25 (m, 2 H), 4.68 (m, 2 H), 5.19 (dd, 1 H, *J* = 3.0, 6.0 Hz), 5.34 (dd, 1 H, *J* = 3.3, 9.0 Hz) 5.42 (dd, 1 H, *J* = 4.2, 9.0 Hz), 5.82 (dd, 1 H, *J* = 2.4, 6.0 Hz), 6.15 (dd, 1 H, *J* = 3.6, 6.0 Hz), 6.32 (dd, 1 H, *J* = 3.6, 6.0 Hz), 7.21–7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 18.3, 18.4, 33.5, 35.0, 44.8, 45.1, 45.4, 45.6, 47.5, 49.5, 49.9, 51.4, 55.7, 56.2, 67.7, 67.8, 123.8, 123.9, 126.6, 126.7, 127.1, 127.2, 128.5, 129.0, 137.3, 137.5, 137.6, 137.7, 151.6, 151.7, 171.5, 171.9; UV (EtOH) λ_{max} (ϵ) 251 (369).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 73.06; H, 6.74; N, 4.51.

(4*S*)-3-(((3'*R*,4'*R*,5'*S*,6'*S*)-5'-Propylbicyclo[2.2.1]hepten-4'-yl)carbonyl)-4-(phenylmethyl)-2-oxazolidinone (6):[26] 95%; R_f 0.77 (silica gel, 2:1 hexanes–EtOAc); GC (DB1701 (30 m × 0.25 mm) 200 °C (1 min), 25 °C per min, 260 °C (15 min), FID 300 °C) assayed as the reduced derivative from exhaustive catalytic hydrogenation t_R minor endo 14.03 min, t_R major endo 14.52 min, t_R minor exo 14.86 min, t_R major exo 15.07 min; mass spectrum, *m/e* 340 (M + 1); IR ($CHCl_3$) 2962, 1778, 1696, 1351, 1205 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 7.0 Hz), 1.37 (m, 5 H), 1.69 (d, 1 H, *J* = 8.6 Hz), 2.04 (m, 1 H), 2.67 (m, 2 H), 3.22 (dd, 1 H, *J* = 3.2, 13.2 Hz), 3.36 (br s, 1 H), 3.57 (t, 1 H, *J* = 3.9 Hz), 4.17 (m, 2 H), 4.66 (m, 1 H), 5.85 (dd, 1 H, *J* = 2.7, 5.4 Hz), 6.41 (dd, 1 H, *J* = 3.2, 5.4 Hz), 7.16–7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.3, 37.8, 38.2, 42.3, 47.3, 47.6, 47.8, 50.5, 55.3, 66.1, 127.3, 129.0, 129.4, 130.9, 135.4, 139.9, 153.4, 174.3; UV (EtOH) λ_{max} (ϵ) 258 (374); $[\alpha]_{589}$ +206.0° (*c* 1.00, MeOH).

Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.31; H, 7.17; N, 4.09.

(4*S*)-3-(((3'*R*,4'*R*,5'*S*,6'*S*)-5'-(1(*E*)-Propenyl)bicyclo[2.2.1]hepten-4'-yl)carbonyl)-4-(phenylmethyl)-2-oxazolidinone (8):[26] 75%; R_f (silica gel, 3:1 hexanes–EtOAc); GC (DB1701 (30 m × 0.25 mm) 200 °C (1 min), 25 °C per min, 260 °C (15 min), FID 300 °C) assayed as the reduced derivative from exhaustive catalytic hydrogenation t_R minor endo 14.03 min, t_R major endo 14.52 min, t_R minor exo 14.86 min, t_R major exo 15.07 min; mass spectrum, *m/e* 338 (M^+); IR ($CHCl_3$) 1779, 1696, 1384, 1231 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (m, 1 H), 1.64 (d, 3 H), 1.72 (m, 1 H), 2.68 (m, 2 H), 3.21 (dd, 1 H, *J* = 3.1, 13.2 Hz), 3.42 (br s, 1 H), 3.74 (t, 1 H, *J* = 3.9 Hz), 4.14 (m, 3 H), 4.64 (m, 1 H), 5.47 (m, 2 H), 5.86 (dd, 1 H, *J* = 2.7, 5.5 Hz), 6.42 (dd, 1 H, *J* = 3.1, 5.5 Hz), 7.18–7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.9, 38.1, 44.9, 47.4, 47.7, 49.8, 50.2, 55.3, 66.1, 125.4, 127.3, 128.9, 129.3, 131.5, 134.0, 135.3, 139.5, 153.3, 173.6; UV (EtOH) λ_{max} (ϵ) 263 (303); $[\alpha]_{589}$ +228.0° (*c* 1.01, MeOH).

Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.47; H, 6.95; N, 3.95.

(4*S*)-3-(((3'*R*,4'*R*,5'*S*,6'*S*)-5'-((Benzyloxy)methyl)bicyclo[2.2.1]hepten-4'-yl)carbonyl)-4-(phenylmethyl)-2-oxazolidinone (12):[26] 86%; R_f 0.77 (silica gel, 1:1 hexanes–EtOAc); HPLC (Supelco LC-18-DB, 25 × 0.46 cm, 60:40 acetonitrile–water, 2.0 mL per min) t_R minor endo 12.95 min, t_R major endo 15.36 min, t_R minor exo 16.85 min, t_R major exo 18.22 min; mass spectrum, *m/e* 418 (M^+); IR ($CHCl_3$) 1778, 1698, 1385 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (m, 1 H), 1.67 (m, 1 H), 2.42 (m, 1 H), 2.69 (dd, 1 H, *J* = 9.8, 13.2 Hz), 2.85 (br s, 1 H), 3.22 (dd, 1 H, *J* = 3.3, 13.2 Hz), 3.39 (br s, 1 H), 3.49 (d, 2 H, *J* = 7.6 Hz), 3.73 (dd, 1 H, *J* = 3.5, 4.4 Hz), 4.13 (m, 2 H), 4.54 (s, 2 H), 4.64 (m, 1 H), 5.92 (dd, 1 H, *J* = 2.7, 5.5 Hz), 6.43 (dd, 1 H, *J* = 3.3, 5.5 Hz), 7.20–7.41 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 38.1, 42.9, 45.3, 47.0, 47.5, 47.7, 55.4, 66.1, 72.9, 73.5, 127.3, 127.5, 127.6, 128.4, 128.9, 129.4, 131.7, 135.4, 138.5, 139.5, 153.4, 173.7; UV (EtOH) λ_{max} (ϵ) 251 (675); $[\alpha]_{589}$ +176.6° (*c* 1.01, MeOH).

Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.54; H, 6.58; N, 3.25.

(4*S*)-3-(((3'*R*,4'*R*,5'*S*,6'*S*)-5'-(Bromomethyl)bicyclo[2.2.1]hepten-4'-yl)carbonyl)-4-(phenylmethyl)-2-oxazolidinone (14):[26] 91%; R_f 0.64 (silica gel, 2:1 hexanes–EtOAc); HPLC (Supelco LC-18-DB, 25 × 0.46 cm, 45:55 H_2O–CH_3CN, 1.0 mL per min) t_R minor endo 16.96 min, t_R major endo 18.46 min, t_R minor exo 21.20 min, t_R major exo 23.58 min; mass spectrum, *m/e* 390 (M^+); IR ($CHCl_3$) 1779, 1699 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (m, 1 H), 1.69 (m, 1 H), 2.61 (m, 1 H), 2.70 (dd, 1 H, *J* = 9.8, 13.2 Hz), 2.85 (br s, 1 H), 3.21 (dd, 1 H, *J* = 3.3, 13.2 Hz), 3.37 (t, 1

(26) The numbering for the bicyclo[2.2.1]heptane ring system is that used in ref 8. It differs from the standard numbering for the bicyclo[2.2.1]heptane ring system.

H, J = 9.6 Hz), 3.44 (br s, 1 H), 3.49 (dd, 1 H, J = 7.1, 9.7 Hz), 3.76 (dd, 1 H, J = 3.6, 4.4 Hz), 4.18 (m, 2 H), 4.68 (m, 1 H), 5.93 (dd, 1 H, J = 2.8, 5.5 Hz), 6.43 (dd, 1 H, J = 3.2, 5.5 Hz), 7.19–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 37.3, 38.1, 46.0, 47.3, 47.4, 47.5, 50.5, 55.4, 66.3, 127.4, 129.0, 129.4, 132.2, 135.3, 139.2, 153.4, 172.9; UV (EtOH) λ_{max} (ϵ) 258 (269); $[\alpha]_{589}$ +127.1° (c 1.02, MeOH).

Anal. Calcd for $C_{19}H_{20}NO_3Br$: C, 58.47; H, 5.16; N, 3.58. Found: C, 58.77; H, 5.28; N, 3.55.

(4*S*)-3-(((3′*R*,4′*R*,5′*S*,6′*S*)-5′-(2-Furanyl)bicyclo[2.2.1]-hepten-4′-yl)carbonyl)-4-(phenylmethyl)-2-oxazolidinone (16):[26] 81%; R_f 0.70 (silica gel, 1:1 hexanes–EtOAc); HPLC (Zorbax NH_2, 25 × 0.46 cm, 99.0:1.0 hexanes–n-PrOH, 1.5 mL per min) t_R minor endo 7.50 min, t_R major endo 8.68 min, t_R minor exo 9.13 min, t_R major exo 10.74 min; mass spectrum, m/e 364 (M + 1); IR ($CHCl_3$) 1780, 1696, 1386 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (m, 1 H), 1.94 (m, 1 H), 2.72 (dd, 1 H, J = 9.8, 13.2 Hz), 3.06 (br s, 1 H), 3.23 (dd, 1 H, J = 3.3, 13.2 Hz), 3.35 (d, 1 H, J = 4.5 Hz), 3.54 (br s, 1 H), 4.17 (m, 2 H), 4.22 (m, 1 H), 4.68 (m, 1 H), 5.96 (dd, 1 H, J = 2.7, 5.5 Hz), 6.08 (d, 1 H, J = 3.1 Hz), 6.28 (dd, 1 H, J = 2.0, 2.8 Hz), 6.50 (dd, 1 H, J = 3.2, 5.5 Hz), 7.21–7.37 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 38.2, 40.9, 47.2, 48.7, 49.1, 49.2, 55.3, 66.3, 105.0, 110.1, 127.4, 129.0, 129.4, 132.1, 135.3, 139.3, 141.4, 153.3, 157.4, 173.2; UV (EtOH) λ_{max} (ϵ) 208 (22 100); $[\alpha]_{589}$ +242.2° (c 1.02, MeOH).

Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.64; H, 5.74; N, 3.79.

(4*S*)-3-(((3′*R*,4′*R*,5′*S*,6′*S*)-5′-(Ethoxycarbonyl)bicyclo-[2.2.1]hepten-4′-yl)carbonyl)-4-(phenylmethyl)-2-oxazolidinone (18):[26] 89%; R_f 0.77 (silica gel, 1:1 hexanes–EtOAc); HPLC (Supelco LC-18-DB, 25 × 0.46 cm, 50:50 acetonitrile–water, 2.0 mL per min) t_R minor endo 17.80 min, t_R major endo 19.87 min, t_R minor exo 21.70 min, t_R major exo 24.06 min; mass spectrum, m/e 270 (M + 1); IR ($CHCl_3$) 1781, 1723, 1697, 1386 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.1 Hz), 1.51 (m, 1 H), 1.76 (m, 1 H), 2.67 (dd, 1 H, J = 9.9, 13.2 Hz), 2.92 (dd, 1 H, J = 1.5, 4.7 Hz), 3.19 (m, 1 H), 3.23 (br s, 1 H), 3.52 (br s, 1 H), 4.16 (m, 4 H), 4.35 (m, 1 H), 4.66 (m, 1 H), 5.95 (dd, 1 H, J = 2.8, 5.5 Hz), 6.40 (dd, 1 H, J = 3.2, 5.5 Hz), 7.17–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 38.2, 46.6, 46.9, 47.8, 48.0, 48.6, 55.3, 60.8, 66.3, 127.4, 129.0, 129.4, 133.1, 135.3, 138.6, 153.1, 172.8, 174.2; UV (EtOH) λ_{max} (ϵ) 251 (262); $[\alpha]_{589}$ +191.9° (c 1.00, MeOH).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.16; H, 6.16; N, 3.75.

3,3′-((3″*R*,4″*R*,5″*S*,6″*S*)-Bicyclo[2.2.1]heptene-4″,5″-diyldicarbonyl)bis(4(*S*)-(phenylmethyl)-2-oxazolidinone) (20):[26] 84%; mp 184–185 °C; R_f 0.82 (silica gel, 1:1 hexanes–EtOAc); HPLC (Zorbax NH_2, 25 × 0.46 cm, 95.0:1.0 hexanes–n-PrOH, 1.5 mL per min) t_R minor endo 1.36 min, t_R major endo 2.98 min; mass spectrum, m/e 501 (M + 1); IR ($CHCl_3$) 1782, 1692, 1388 cm^{-1}; NMR ($CDCl_3$) δ 1.51 (m, 1 H), 1.88 (m, 1 H), 2.70 (dd, 1 H, J = 9.9, 13.3 Hz), 2.83 (dd, 1 H, J = 9.4, 13.3 Hz), 3.14 (br s, 1 H), 3.25 (m, 2 H), 3.50 (br s, 1 H), 3.83 (d, 1 H, J = 4.8 Hz), 4.08–4.29 (m, 4 H), 4.57 (m, 1 H), 4.67 (m, 2 H), 6.12 (dd, 1 H, J = 2.7, 5.4 Hz), 6.46 (dd, 1 H, J = 3.2, 5.4 Hz), 7.19–7.42 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 38.0, 38.1, 46.8, 47.2, 47.4, 49.3, 55.4, 55.5, 66.3, 66.4, 127.3, 127.4, 128.9, 129.0, 129.4, 129.5, 134.7, 135.2, 135.3, 137.9, 153.4, 172.9, 173.7; UV (EtOH) λ_{max} (ϵ) 204 (21 000); $[\alpha]_{589}$ +399.5° (c 1.00, MeOH).

Anal. Calcd for $C_{29}H_{28}N_2O_6$: C, 69.59; H, 5.64; N, 5.60. Found: C, 69.45; H, 5.74; N, 5.51.

1,3-*O*-Benzylidene-1,3-propanediol (22a). 1,3-Propanediol (21) (76.5 g, 1.0 mol) was dissolved in toluene (250 mL) and treated with benzaldehyde (107.1 g, 1 mol) and a catalytic amount of p-toluenesulfonic acid monohydrate (300 mg). The resulting solution was stirred at reflux under a Dean–Stark trap until the theoretical amount of water (18 mL) had separated (2.5 h). The reaction mixture was cooled to room temperature. Although the crude acetal was used directly in the subsequent reduction, the product had the following characteristics: NMR ($CDCl_3$) δ 1.45 (m, 1 H), 2.25 (m, 1 H), 3.99 (dt, 2 H, J = 3.0, 12.8 Hz), 4.29 (m, 2 H), 5.51 (s, 1 H), 7.32–7.56 (m, 5 H); R_f 0.73 (silica gel, 2:1 hexanes–EtOAc).

3-(Benzyloxy)-1-propanol (22). The toluene solution of the benzylidene acetal was cooled to 0 °C under nitrogen. Diisobutylaluminum hydride (775 mL, 1.6 M in toluene) was then added dropwise with vigorous stirring at a rate to maintain the temperature at 0 ● 5 °C. After the addition was complete, the reaction mixture was allowed to stir at room temperature overnight. A solution of MeOH (140 mL) in toluene (240 mL) was then added carefully with cooling at a rate to keep the temperature below 40 °C (*caution*: exothermic with vigorous gas evolution!). After all of the methanol solution was added, the reaction mixture became thick and gelatinous. Water (70 mL) was then carefully added (more gas evolution), and the resulting slurry was stirred under the mixture became granular (1 h). The precipitate was filtered through Celite and washed with toluene, and the filtrate was concentrated to an oil. Distillation of the crude oil afforded 3-(benzyloxy)-1-propanol (147.9 g) in 89% yield as a colorless liquid: bp 135–139 °C (2 mmHg) (lit.[14] bp 110 °C (0.1 mm) and 110 °C (0.5 mm); NMR ($CDCl_3$) δ 1.87 (m, 2 H), 2.37 (br s, 1 H, exch D_2O), 3.67 (t, 2 H, J = 5.8 Hz), 3.78 (m, 2 H), 4.54 (s, 2 H), 7.26 (m, 5 H); R_f 0.23 (silica gel, 2:1 hexanes–EtOAc).

Methyl 5-(Benzyloxy)-2(*E*)-pentenoate (23). Oxalyl chloride (102.6 mL, 1.18 mol) was dissolved in CH_2Cl_2 (500 mL) in a 5-L 3-neck round-bottom flask equipped with a dropping funnel, mechanical stirrer, N_2 inlet, and thermocouple. The reaction mixture was cooled in an acetone/dry ice bath to an internal temperature of approximately −70 °C. A solution of dimethyl sulfoxide (115.6 mL, 1.63 mol) in CH_2Cl_2 (100 mL) was then added dropwise with stirring. When the addition was complete, the mixture was stirred at this temperature for an additional 15 min, followed by the dropwise addition of the alcohol **2** (150.4 g, 0.91 mol) dissolved in CH_2Cl_2 (200 mL). The resulting mixture was stirred at −65 °C to −70 °C for 45 min. Triethylamine (353 mL, 2.53 mol) was then added, and the reaction mixture became very thick with precipitate. After another 10 min, a solution of the methyl (triphenylphosphoranylidene)acetate (319.8 g, 0.96 mol) in CH_2Cl_2 (600 mL) was added. The reaction mixture was stirred at this temperature for 15 min, the cooling bath was removed, and stirring was continued at room temperature for 4 h. CH_2Cl_2 (1 L) was added, and the mixture was washed successively with water (2 × 1 L), $NaHCO_3$ (1 L), and brine (1 L) and dried (Na_2SO_4). The dessicant was filtered, and the filtrate was concentrated to dryness in vacuo. The residue was triturated with hexanes (1 L) and stirred at room temperature for 2 h. The precipitated $Ph_3P{=}O$ was filtered and washed with hexanes (2 × 150 mL), and the filtrate was concentrated to a dark amber oil. The amber oil was distilled to afford the α,β-unsaturated ester **23** as a light yellow oil, 181.2 g (90.4%): bp 140 °C (0.9 mmHg); R_f 0.66 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, m/e 220 (M^+); IR ($CHCl_3$) 3013, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.48 (m, 2 H), 3.56 (t, 2 H, J = 6.4 Hz), 3.70 (s, 3 H), 4.49 (s, 2 H), 5.89 (dt, 1 H, J = 1.3, 15.6 Hz), 6.89 (dt, 1 H, J = 7.0, 15.6 Hz), 7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 32.5, 51.3, 68.1, 72.9, 122.3, 127.5, 128.2, 131.9, 137.9, 145.8, 166.7; UV (EtOH) λ_{max} (ϵ) 246 (9110), 206 (13 400).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.83; H, 7.51.

5-(Benzyloxy)-2(*E*)-pentenoic Acid (24). The ester **23** (199 g, 0.91 mol) was dissolved in THF (400 mL) and treated with 1 N NaOH (1.36 L). The heterogeneous mixture was stirred vigorously at room temperature for 5 h. The reaction mixture was diluted with ether (1 L), and the phases were separated. The aqueous phase was washed further with ether (2 × 400 mL); 6 N HCl was added dropwise to the aqueous phase to pH 3, followed by extraction with CH_2Cl_2 (3 × 400 mL), and the organic phase was dried (Na_2SO_4). The dessicant was filtered, and the filtrate was concentrated to a pale yellow liquid: R_f 0.05 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, m/e 206 (M^+); IR ($CHCl_3$) 3031, 2865, 1699, 1656, 1421, 1224 cm^{-1}; NMR ($CDCl_3$) δ 2.52 (m, 2 H), 3.58 (t, 2 H, J = 6.6 Hz), 4.52 (s, 2 H), 5.90 (m, 1 H), 7.10 (dt, 1 H, J = 7.2, 15.6 Hz), 7.31 (m, 5 H), 11.58 (br s, exchanges with D_2O); ^{13}C NMR ($CDCl_3$) δ 31.9, 67.3, 72.3, 121.6, 127.0, 127.1, 127.7, 137.2, 147.8, 171.1; UV (EtOH) λ_{max} (ϵ) 257 (440), 204 (19 100).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.80; H, 6.85.

(4*S*)-3-((*E*)-5′-(Benzyloxy)-2′-pentenoyl)-4-(phenylmethyl)-2-oxazolidinone (9). A flask as described for **23** was charged with the acid **24** (140.7 g, 0.68 mol), dry THF (2 L), and triethylamine (144 mL, 1.03 mol). The resulting solution was cooled to −50 °C under a nitrogen atmosphere. Freshly distilled pivaloyl chloride (84.0 mL, 0.68 mol) was then added dropwise

over 30 min. When the addition was complete, the reaction mixture was allowed to warm to −30 °C to −20 °C, and this temperature was maintained while the subsequent deprotonation was conducted. In a separate 3-L flask was dissolved the (*S*)-4-benzyl-2-oxazolidinone (110 g, 0.62 mol) in anhydrous THF (1.2 L) under nitrogen. The flask was cooled in a CO_2/acetone bath, and *n*-BuLi (400 mL, 0.64 mol) was added dropwise. When the addition of was complete, the homogeneous solution was stirred at −78 °C for 30 min. The solution of the lithium oxazolidinone (X_PLi) was then transferred to the heterogeneous suspension of the mixed anhydride via cannula at −78 °C with vigorous stirring. After stirring at this temperature for 30 min, the reaction mixture was slowly brought to room temperature with continued stirring for 6 h. Saturated NH_4Cl solution (700 mL) was added, and most of the THF was removed in vacuo. The mixture was extracted with EtOAc (1.5 L), and the organic phase was washed successively with saturated aqueous $NaHCO_3$ (3 × 500 mL), H_2O (500 mL), and brine (500 mL) and dried (Na_2SO_4). The dessicant was removed by filtration, and the filtrate was concentrated to an orange oil, 219.8 g. The crude material was used directly in the next step without purification, but an analytical sample was prepared by chromatography over SiO_2 with hexanes–EtOAc (4:1): R_f 0.52 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, *m/e* 365 (M^+); IR ($CHCl_3$) 1778, 1683, 1637, 1356 cm^{-1}; NMR ($CDCl_3$) δ 2.56 (br q, 2 H, *J* = 6.0 Hz), 2.95 (dd, 1 H, *J* = 7.8, 13.5 Hz), 3.07 (dd, 1 H, *J* = 3.0, 13.5 Hz), 3.60 (t, 2 H, *J* = 6.0 Hz), 4.19 (dd, 1 H, *J* = 2.4, 8.4 Hz), 4.35 (t, 1 H, *J* = 8.4 Hz), 4.51 (s, 2 H), 4.72 (m, 1 H), 7.05–7.24 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 32.5, 36.7, 54.5, 66.1, 68.0, 71.9, 121.7, 126.9, 127.4, 127.5, 128.2, 128.6, 129.5, 135.7, 138.4, 147.5, 153.3, 164.1; UV (EtOH) λ_{max} (ε) 228 (15 600), 209 (21 100); $[\alpha]_{589}$ +44.1° (*c* 1.01, MeOH).

Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.55; H, 6.59; N, 3.83.

(4*S*)-3-(((3′*R*,4′*R*,5′*S*,6′*S*)-5′-(2-(Benzyloxy)ethyl)bicyclo[2.2.1]hepten-4′-yl)carbonyl)-4-(phenylmethyl)-2-oxazolidinone (10).[26] A flask as described for **23** was charged with the imide **9** (350.8 g, 0.96 mol) and CH_2Cl_2 (1.35 L) and cooled to −78 °C under N_2. The addition funnel was charged with Et_2AlCl (170.0 mL, 1.34 mol) and diluted with CH_2Cl_2 (150 mL). This solution was then added dropwise to the imide at a rate to maintain the temperature below −70 °C (30 min). After the Et_2AlCl was added, freshly distilled cyclopentadiene (240.0 mL, 3.0 mol) was added dropwise at a rate to maintain the temperature below −75 °C (15 min). Stirring was continued at −78 °C for 5 h, whereupon chromatographic analysis indicated complete conversion to the adduct. The reaction mixture at −78 °C was transferred via cannula (12 gauge, Teflon) into a rapidly stirring solution of 1 N HCl at 0 °C (40 min; *note*: strong gas evolution!). After the quench was complete, the layers were separated, and the organic phase was washed successively with 1 N HCl (1.4 L), H_2O (1 L), saturated aqueous $NaHCO_3$ (1 L), and brine (1 L) and dried (Na_2SO_4). Removal of the volatiles afforded a light brown oil, 377 g. The crude material was used directly in the next step without purification, but an analytical sample was prepared by chromatography over SiO_2 with hexanes–EtOAc (4:1): R_f 0.66 (silica gel, 2:1 hexanes–EtOAc); HPLC (Supelco LC-18-DB, 25 × 0.46 cm, 60:40 acetonitrile–water, 2.0 mL per min) t_R minor endo 18.10 min, t_R major endo 20.05 min, t_R minor exo 22.64 min, t_R major exo 25.15 min; mass spectrum, *m/e* 431 (M^+); IR ($CHCl_3$) 3019, 1778, 1696, 1385, 1226 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (m, 1 H), 1.71 (m, 1 H), 1.85 (q, 2 H, *J* = 6.0 Hz), 2.14 (m, 1 H), 2.32 (dd, 1 H, *J* = 9.6, 13.2 Hz), 2.68 (m, 1 H), 3.15 (dd, 1 H, *J* = 3.6, 13.5 Hz), 3.37 (br s, 1 H), 3.54 (m, 2 H), 3.73 (m, 2 H), 3.99 (dd, 1 H, *J* = 2.9, 9.0 Hz), 4.43 (m, 3 H), 5.84 (dd, 1 H, *J* = 2.7, 5.6 Hz), 6.41 (dd, 1 H, *J* = 3.2, 5.6 Hz), 7.16–7.64 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 35.3, 37.9, 40.2, 47.1, 47.5, 48.3, 50.5, 54.9, 65.6, 70.3, 72.6, 126.9, 127.0, 127.1, 128.1, 128.6, 129.1, 130.8, 135.2, 138.5, 139.3, 153.0, 173.8; UV (EtOH) λ_{max} (ε) 257 (480); $[\alpha]_{589}$ +180.6° (*c* 1.01, MeOH).

Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.19; H, 6.95; N, 3.26.

(4*S*)-3-(((3′*R*,4′*R*,5′*S*,6′*S*)-5′-(2-(Benzyloxy)ethyl)bicyclo[2.2.1]heptan-4′-yl)carbonyl)-4-(phenylmethyl)-2-oxazolidinone (25).[26] The adduct **10** (137 g, 0.32 mol) was dissolved in EtOAc (750 mL) and transferred to a 2-L Parr bottle containing 5% Pt/C (25 g) under N_2. The vessel was degassed (evacuated/H_2 purge, 5×). The reduction was accomplished by agitation under 36 psi of H_2 at room temperature for 2 h. The catalyst was removed by filtration through Celite and washed with EtOAc, and the filtrate was concentrated to dryness to afford 139 g. The crude material was used directly in the next step without purification, but an analytical sample was prepared by chromatography over SiO_2 with hexanes–EtOAc (4:1): R_f 0.67 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, *m/e* 433 (M^+); IR ($CHCl_3$) 2957, 1778, 1692, 1237, 1198 cm^{-1}; NMR ($CDCl_3$) δ 1.21–1.46 (m, 4 H), 1.51–1.76 (m, 4 H), 2.07 (m, 1 H), 2.24 (m, 1 H), 2.63 (dd, 1 H, *J* = 9.8, 13.2 Hz), 2.78 (br s, 1 H), 3.24 (dd, 1 H, *J* = 3.0, 13.2 Hz), 3.40–3.56 (m, 3 H), 3.74 (t, 1 H, *J* = 8.4 Hz), 3.98 (dd, 1 H, *J* = 3.0, 9.8 Hz), 4.42 (m, 2 H), 4.49 (m, 1 H), 7.14–7.35 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 23.5, 29.8, 35.9, 38.3, 40.9, 41.7, 42.7, 53.4, 54.4, 55.1, 65.7, 70.1, 72.8, 127.1, 127.2, 127.3, 128.3, 128.9, 129.3, 135.5, 138.7, 153.0, 174.0; UV (EtOH) λ_{max} (ε) 205 (20 300); $[\alpha]_{589}$ +117.3° (*c* 1.01, MeOH).

Anal. Calcd for $C_{27}H_{31}NO_4$: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.53; H, 6.98; N, 3.26.

(3′*R*,4′*R*,5′*S*,6′*S*)-5-(2-(Benzyloxy)ethyl)-4′-carboxybicyclo[2.2.1]heptane (26).[26] The imide **25** (139 g, 0.32 mol) was placed in a 3-L 3-neck round-bottom flask equipped with a mechanical stirrer, thermocouple probe, and a side arm left open to the atmosphere. The imide was dissolved by the addition THF (1.4 L, reagent grade), followed by water (650 mL, deionized). The flask was cooled in an ice bath so that the internal temperature was 3 ± 2 °C; 30% H_2O_2 (205 mL, 2.0 mol) was added to the mixture. Solid $LiOH·H_2O$ (42.0 g, 1.0 mol) was then added slowly with vigorous stirring (important), causing the internal temperature to rise 3 °C. The reaction mixture was stirred at 330 rpm at 3 ± 2 °C for 10 h. $NaHSO_3$ (170 g) was then added portionwise at a rate to maintain the internal temperature below 20 °C. When the addition was complete, the mixture was stirred for 30 min with cooling (ice bath). The reaction mixture was partitioned between 1 N NaOH (1 L) and Et_2O (2 L). The organic phase was extracted with 1 N NaOH (3 × 500 mL), and the combined aqueous phase was washed with Et_2O (2 × 500 mL). The pH of the aqueous phase was adjusted to 3 with 6 N HCl and exhaustively extracted with CH_2Cl_2, and the extracts were dried (Na_2SO_4). The filtrate was concentrated to a colorless oil, 80.6 g (87.9%), and was chromatographically homogeneous. An analytical sample was prepared by chromatography over SiO_2 with hexanes–EtOAc (2:1): R_f 0.41 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, *m/e* 275 (M + 1); IR ($CHCl_3$) 3017, 1702, 1455, 1308, 1237, 1096 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (m, 2 H), 1.41 (m, 2 H), 1.52 (m, 3 H), 1.65 (m, 1 H), 1.92 (br q, 1 H, *J* = 6.6 Hz), 2.03 (m, 1 H), 2.42 (t, 1 H, *J* = 4.2 Hz), 2.56 (m, 1 H), 3.48 (t, 2 H, *J* = 6.6 Hz), 4.46 (s, 2 H), 7.22–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.3, 29.5, 36.2, 37.5, 40.9, 41.8, 42.2, 54.2, 69.3, 73.2, 127.6, 127.8, 128.5, 138.5, 180.8; UV (EtOH) λ_{max} (ε) 206 (6910); $[\alpha]_{589}$ +19.0° (*c* 1.01, MeOH).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.52; H, 8.11.

The Et_2O extracts from above were combined and concentrated to dryness. Recrystallization from toluene afforded the (*S*)-4-benzyl-2-oxazolidinone (53.3 g, 90.0%) which had perfect spectral (NMR, α_D) and chromatographic (TLC, HPLC) data and was recycled.

(3′*R*,4′*R*,5′*S*,6′*S*)-5-(2-(Benzyloxy)ethyl)-4′-benzenesulfonamidobicyclo[2.2.1]heptane (29).[26] The acid **26** (80.5 g, 0.293 mol) was dissolved in acetone (400 mL) and placed in a 1-L flask as described for **23**. Triethylamine (45.0 mL, 0.323 mol) was added, and the flask was cooled to 0 °C. Ethyl chloroformate (30.9 mL, 0.323 mol) was added dropwise, causing the internal temperature to rise to 17 °C with a concomitant precipitation of $Et_3N·HCl$. Water (40 mL) was added, and the resulting solution was stirred with ice cooling for 1 h. TLC analysis showed complete conversion to a very nonpolar material. A solution of NaN_3 (30.5 g, 0.47 mol) in H_2O (75 mL) was then added dropwise with continued stirring for 1 h. The reaction mixture was diluted with H_2O (400 mL) and extracted with toluene (3 × 300 mL). The combined organic phase was washed with brine (300 mL), dried (Na_2SO_4), filtered, and concentrated to ca. half volume in vacuo (to remove the acetone). The toluene solution was then slowly brought to reflux, with a very vigorous evolution of N_2 noted. After 1.5 h, the yellow solution was cooled to room temperature and concentrated to dryness. The oily yellow residue

was dissolved in THF (300 mL) and cooled to 0 °C under N_2. Concentrated H_2SO_2 (30 mL) was added dropwise, resulting in the evolution of CO_2 gas. After 30 min, the aqueous solution was partitioned between E_2O (300 mL) and 2 N HCl (100 mL), and the layers were separated. The organic phase was extracted with 2 N HCl (2 × 100 mL), and the combined aqueous phase was washed with Et_2O (2 × 100 mL). The pH of the aqueous phase was adjusted to 10 by the addition of 6 N NaOH. Extraction of the aqueous phase with CH_2Cl_2 (3 × 150 mL), which was dried (Na_2SO_4) and concentrated to dryness, afforded the crude amine (61.0 g, 84%). The crude amine **28** was dissolved in CH_2Cl_2 (300 mL), treated with Et_3N (104.0 mL, 0.75 mol), and cooled to 0 °C under N_2. Benzenesulfonyl chloride (34.9 mL, 0.27 mol) was then added dropwise with stirring. After 30 min at 0 °C and 1.5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (200 mL), washed successively with 1 N HCl (2 × 300 mL), 2 N NaOH (300 mL), 5% NH_4OH (2 × 300 mL), H_2O (300 mL), and brine (300 mL), and dried (Na_2SO_4). The dessicant was filtered, and the filtrate was concentrated to dryness to afford the crude sulfonamide **29**, 98.0 g, as a heavy colorless oil. The product was chromatographed over SiO_2 (1.5 kg), eluting first with CH_2Cl_2 (1000 mL) and then with 4% MeOH in CH_2Cl_2 (2000 mL). After removal of the volatiles in vacuo and thorough drying under high vacuum, the material obtained in this manner weighed 90.9 g (80.5% from the acid **26**), as a clear, colorless oil, which crystallized on standing: mp 62–64 °C; R_f 0.55 (silica gel, 2:1 hexanes–EtOAc); mass spectrum, m/e 385 (M^+); IR ($CHCl_3$) 3029, 2876, 1448, 1165 cm^{-1}; NMR ($CDCl_3$) δ 1.09–1.39 (m, 6 H), 1.55 (m, 3 H), 1.87 (m, 1 H), 2.18 (br s, 1 H), 3.02 (m, 1 H), 3.29 (m, 2 H), 4.40 (m, 2 H), 4.78 (d, 1 H, J = 5.5 Hz, exch D_2O), 7.31 (m, 5 H), 7.48 (m, 3 H), 7.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 30.1, 34.7, 35.2, 41.0, 41.1, 47.1, 62.0, 67.9, 72.9, 127.2, 127.6, 127.7, 128.4, 129.0, 132.5, 138.4, 140.7; UV (EtOH) λ_{max} (ϵ) 258 (607); $[\alpha]_{589}$ +0.39° (c 1.01, MeOH).

Anal. Calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.42; H, 7.11; N, 3.70.

(3′*R*,4′*R*,5′*S*,6′*S*)-5′-(2-Hydroxyethyl)-4′-benzenesulfonamidobicyclo[2.2.1]heptane (30).[26] The benzyl ether **29** (63.0 g, 0.16 mol) was dissolved in 95% EtOH (300 mL) and transferred to a Parr bottle containing 10% Pd on C (10.0 g) under N_2, 6 N HCl (9.0 mL) was added, and the mixture was shaken under 40–45 psi of H_2 over 18 h. The catalyst was removed by filtration over Celite and washed with 95% EtOH, and the filtrate was concentrated to dryness in vacuo. The residue was azeotroped from toluene (3 × 300 mL) in vacuo. Recrystallization from hot toluene (250 mL) afforded the alcohol **30** as elongated plates, 40.7 g (84.4%): mp 120–122 °C; R_f 0.34 (silica gel, 1:1 hexanes–EtOAc); mass spectrum, m/e 295 (M^+); IR ($CHCl_3$) 3030, 2958, 1448, 1322, 1164 cm^{-1}; NMR ($CDCl_3$) δ 1.19 (m, 4 H), 1.36 (m, 2 H), 1.54 (m, 3 H), 1.87 (m, 1 H), 2.06 (br s, 1 H), 2.48 (br s, 1 H), 3.06 (m, 1 H), 3.53 (m, 2 H), 5.76 (d, 1 H, J = 6.6 Hz, exch D_2O), 7.55 (m, 3 H), 7.93 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.6, 30.0, 35.2, 37.4, 40.8, 41.0, 46.2, 60.2, 61.9, 127.2, 129.0, 132.6, 140.6; UV (EtOH) λ_{max} (ϵ) 223 (6680); $[\alpha]_{589}$ +26.7° (c 1.01, MeOH).

Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 61.23; H, 7.32; N, 4.71.

(3′*R*,4′*R*,5′*S*,6′*S*)-5′-(Formylmethyl)-4′-benzenesulfonamidobicyclo[2.2.1]heptane (31).[26] A 1-L flask was equipped as described for **23**. Freshly distilled CH_2Cl_2 (200 mL) was added, followed by the addition of oxalyl chloride (8.9 mL, 0.102 mol). The solution was cooled to −78 °C under N_2, and then a solution of DMSO (12.0 mL, 0.169 mol) in CH_2Cl_2 (20 mL) was added dropwise. The mixture was stirred at −78 °C for 10 min, and then a solution of the alcohol **30** (25.0 g, 0.0847 mol) in CH_2Cl_2 (200 mL) was added dropwise. The reaction mixture was stirred vigorously at −78 °C for 45 min. Triethylamine (59.0 mL, 0.423 mol) was added dropwise, and the mixture was stirred for an additional 10 min at −78 °C, followed by removal of the cooling bath with continued stirring. When the internal temperature had reached 0 °C, the reaction mixture was partitioned between H_2O (400 mL) and CH_2Cl_2 (200 mL). The layers were separated, and the organic phase was washed with H_2O (400 mL) and brine (400 mL) and dried (Na_2SO_4). Filtration and removal of the volatiles afforded the aldehyde **31** as an pale yellow oil, which was used directly in the subsequent Wittig reaction without purification. The aldehyde could be crystallized from toluene, however, to afford the title compound as a colorless, crystalline solid: mp 100–101 °C; R_f 066 (silica gel, 1:1 hexanes–EtOAc); mass spectrum, m/e 294 (M + 1); IR ($CHCl_3$) 2959, 1720, 1448, 1341, 1224, 1158 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (m, 4 H), 1.53 (m, 2 H), 1.85 (m, 1 H), 2.26 (m, 2 H), 2.36 (dd, 2 H, J = 7.2, 9.6 Hz), 2.85 (m, 1 H), 5.62 (m, 1 H), 7.46–7.62 (m, 3 H), 7.88 (m, 2 H), 9.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.6, 29.8, 35.1, 41.2, 44.0, 46.0, 49.3, 62.2, 127.3, 129.0, 132.7, 140.1, 201.7; UV (EtOH) λ_{max} (ϵ) 223 (6540); $[\alpha]_{589}$ +31.8° (c 1.01, $CHCl_3$).

Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.68; H, 6.30; N, 4.87.

(+)-(5*Z*)-7-(3-*endo*-((Phenylsulfonyl)amino)bicyclo[2.2.1]hept-2-*exo*-yl)heptenoic Acid ((+)-S-145). (4-Carboxybutyl)triphenylphosphonium bromide (112.67 g, 0.254 mol) was suspended in freshly distilled THF (590 mL) in a 1-L flask as described for **23**. Potassium *tert*-butoxide (59.4 g, 0.513 mol, 97%) was added portionwise with rapid stirring under N_2. The internal temperature rose to 39 °C, and the resulting bright orange suspension was stirred at room temperature for 1.25 h. The reaction mixture was then cooled to −20 °C (internal temperature), and a solution of the aldehyde (above) in THF (100 mL) was added dropwise over 30 min. The reaction mixture was stirred at −20 °C for 2 h and at room temperature for 1.5 h. The reaction mixture was quenched with 1 N HCl (250 mL) and extracted with EtOAc (3 × 350 mL). The combined organic phase was washed with brine (400 mL) and dried (Na_2SO_4). The dessicant was filtered, and the filtrate was concentrated to dryness. The residue was partitioned between 1 N NaOH (250 mL) and toluene (250 mL). The organic phase was extracted with 1 N NaOH (100 mL) and H_2O (2 × 100 mL). The combined aqueous phase was washed with toluene (2 × 250 mL), and the pH was adjusted to 4 with 3 N HCl, followed by extraction with CH_2Cl_2 (3 × 200 mL). The organic layer was washed with brine (200 mL), dried (Na_2SO_4), filtered, and concentrated to 59.9 g. Flash chromatography over SiO_2 (1.7 kg) with hexanes–EtOAc, 4:1 (2 L) → 2:1 (2 L) → 1:1 (2 L), afforded chromatographically pure (+)-S-145, 21.5 g (67.3%, two steps). Recrystallization from 5.6 volumes of toluene–hexane (3.6:1) afforded colorless, crystalline (+)-S-145: mp 60–62 °C; R_f 0.48 (silica gel, 1:1 PhH–EtOAc); HPLC (Supelco LC-18-DB, 25 × 0.46 cm, 300:200:350:1 acetonitrile–methanol–water–acetic acid, 2.0 mL per min, 240 nm) t_R desired endo 9.24 min, t_R undesired exo 11.26 min; HPLC (Chiracel OD, 25 × 0.46 cm, 9:1 hexane–2-propanol, 1.5 mL per min, 240 nm) as methyl ester t_R undesired enantiomer 10.28 min, t_R desired enantiomer 12.70 min; mass spectrum m/e 378 (M + 1); IR ($CHCl_3$) 3376, 2958, 1709, 1321, 1159 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (m, 1 H), 1.16 (m, 2 H), 1.30 (m, 1 H), 1.38 (m, 1 H), 1.44–1.69 (m, 4 H), 1.73–2.00 (m, 5 H), 2.15 (br s, 1 H), 2.34 (t, 2 H, J = 7.2 Hz), 3.01 (m, 1 H), 5.21 (m, 2 H), 5.45 (d, 1 H, J = 6.6 Hz, exch D_2O), 7.53 (m, 3 H), 7.91 (m, 2 H), 9.50 (br s, 1 H exch D_2O); ^{13}C NMR ($CDCl_3$) δ 20.8, 24.5, 26.4, 29.9, 32.1, 33.3, 35.0, 40.3, 41.2, 50.7, 61.6, 127.2, 128.5, 129.0, 129.8, 132.5, 140.8, 179.2; UV (EtOH) λ_{max} (ϵ) 225 (5270); $[\alpha]_{589}$ +28.7° (c 1.00, MeOH).

Anal. Calcd for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.21; N, 3.71. Found: C, 63.63; H, 6.97; N, 3.95.

The material prepared in this manner was identical in every respect with a sample provided to us by Shionogi.

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