Asymmetric Diels−Alder, Michael, and Aldol Reactions Using a Planar Chiral 1,3-Oxazol-2(3*H*)-one Derived from (*R*)-(+)-4-Hydroxy-[2.2]paracyclophane

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(+)-(*R*)-[2.2]Paracyclophane[4,5-*d*]-1,3-oxazol-2(3*H*)-one exhibiting planar chirality has been used as a chiral auxiliary in asymmetric Diels−Alder, Michael, and aldol reactions of α,β-unsaturated carboxy and enolate imides, respectively. The endo-exo- and face-diastereoselectivity is good and is controlled by the spatial relationship between the prochiral center and the C9−C10 ethylene bridge of the [2.2]paracyclophane moiety. The chiral auxiliary is easily removed and quantitatively recovered.

Introduction

While the importance of Evans chiral auxiliaries (1,3-oxazolidin-2-ones) for asymmetric carbon−carbon formation (Diels−Alder, Michael, and aldol reactions) is well documented,[1] no investigation has been carried out, with the exception of our preliminary communication,[2] on the use of chiral 1,3-oxazolones for asymmetric syntheses. Most chiral 1,3-oxazolidinones have been derived from naturally occurring compounds such as α-amino acids,[3] terpenes,[4] carbohydrates,[5] and tartaric acid,[6] and the chirality is secured by the presence of one or more chiral centers. Moreover, to achieve high diastereo- and enantioselectivities, the presence of an alkyl or aryl substituent at C4 of the 1,3-oxazolidinone ring is essential. This strategy does not seem to be suitable for preparing effectual chiral auxiliaries with a 1,3-oxazolonic moiety. As a part of our research concerning the use of [2.2]-paracyclophane in organic synthesis,[7] we decided to use this compound to prepare 1,3-oxazolones that exhibit planar chirality.

The [2.2]paracyclophane chemistry has attracted the interest of researchers since the middle of the last century.[8] After a standstill period, investigations in this area have received a new impulse[7,9] and recently there has been notable progress especially regarding the synthesis of new derivatives[10] and their application as ligands of organometallic catalysts[11] and as chiral auxiliaries in asymmetric reactions.[10k,n,11c,d,g] Here we report the synthesis of the first planar chiral 1,3-oxazol-2-one

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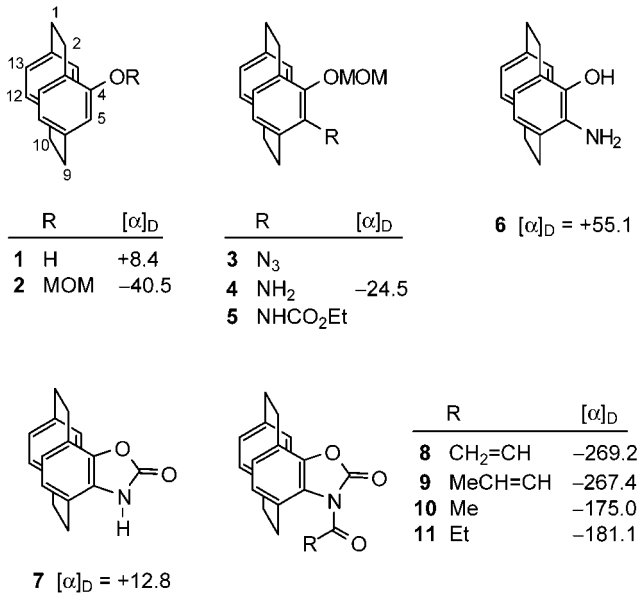
Scheme 1



derived from (+)-(*R*)-4-hydroxy-[2.2]paracyclophane (**1**) and examples of its applications as a chiral auxiliary for asymmetric carbon−carbon bond formation.

Results and Discussion

Synthesis of (+)-(*R*)-[2.2]Paracyclophane-[4,5-*d*]-1,3-oxazol-2-(3*H*)-one. Ortho-directed metalation of MOM-protected hydroxy derivative **2**[7a] (Scheme 1) with butyllithium, followed by nucleophilic attack of the corresponding lithium derivative with TsN_3, gave the 5-azido-derivative **3**. Reduction of **3** with $LiAlH_4$ allowed (−)-(*R*)-4-OMOM-5-amino-[2.2]paracyclophane (**4**) to be isolated. Deprotection of **4** and successive reaction of the resulting hydroxyamino compound **6** with ethyl chloroformate gave (+)-(*R*)-[2.2]paracyclophane-[4,5-*d*]-1,3-oxazol-2-(3*H*)-one (**7**) as a stable and optically pure compound in ca. 20% overall yield from **1**. Transformations of **3** to **4** and **4** to **6** occurred with 95% conversions, but **4** and **6** were isolated in only 56 and 53% yields, respectively. This is mainly due to their low solubility in Et_2O and their reactivity toward solvents such as chloroform, acetone, and ethyl acetate. Therefore, we planned to prepare **7** from **2** without purifying or isolating the intermediates. The crude azido **3** was converted into the amino derivative **4**, which was not isolated but protected in situ by reaction with ethyl chloroformate to give **5** that was directly converted to **7**. Following this procedure allowed preparation of the oxazolone **7** from **1** in 50% overall yield. ^1H and ^{13}C NMR, IR, and elemental analyses (see Experimental Section and Supporting Information) support the structure of **7** and its precursors.

Diels−Alder Reactions. The preparation of dienophiles and the Diels−Alder reaction were performed in an organic solvent according to the Evans procedure.[1d] Reaction of **7** with MeMgBr or BuLi in anhydrous THF followed by acylation with acryloyl chloride or crotonyl chloride gave the unsaturated carboximides **8** and **9**, respectively. Diels−Alder cycloaddition of **8** with cyclopentadiene in CH_2Cl_2 at −100 °C[12] in the presence of Et_2AlCl (1.4 equiv)[13] rapidly afforded (ca. 10 min) a mixture of adducts **A** (R = H) and **C** (R = H) (Scheme 2) with complete endo stereoselectivity and 86:14 endo face-selectivity (Table 1, entry 1).

The Et_2AlCl cycloaddition reaction of (*E*)-crotonyl derivative **9** with the same diene carried out at −78 °C (entry 2) afforded, in 5 min, a mixture of adducts **A** (R = Me), **B** (R = Me), and **C** (R = Me) in 90% yield with an excellent endo/exo ratio (97.8:2.2) and a high level of **A**/**C** endo face-selectivity (97.7:2.3). Uncatalyzed Diels−Alder reaction of **9** (entry 3) was slow (40% conversion, after 30 h); it again occurred with good endo-selectivity (endo/exo = 98:2), but with reversed face-diastereoselection, with the **C** (R = Me) adduct being the main reaction product (85.6%). Using our experience of organic reactions carried out in aqueous media,[14] we also carried out the cycloaddition of **9** with cyclopentadiene in water. This reaction occurred under heterogeneous conditions (entry 4), was slow (42% conversion, after 30 h), and gave the same endo-selectivity (endo/exo = 97.6:2.4) in favor of the **C** (R = Me) adduct, as the reaction performed in sole CH_2Cl_2 at room temperature; only a slightly higher amount of **C**/**A**-endo face-selectivity (91.5:8.5) was observed. By using $InCl_3$ (1.4 equiv) in an aqueous medium, we observed no catalytic effect (entry 5).

The removal of the chiral auxiliary with lithium benzyl oxide in THF (0 °C, 3 h)[1d] was performed with a good yield and occurred with complete recovery of the chiral auxiliary.

The structures of the Diels−Alder adducts are supported by ^1H and ^{13}C NMR spectra (see Experimental

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(12) When the reaction was performed at −78 °C, the reaction yield was only 30% because of the large propensity of acryloyl imide to dimerize.

(13) Et_2AlCl was added before the diene. With reversal of the order, the cycloaddition occurs again with good yield (80%) and endo-selectively (100%) but not face selectivity (**A**/**C** = 54:46).

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Scheme 2

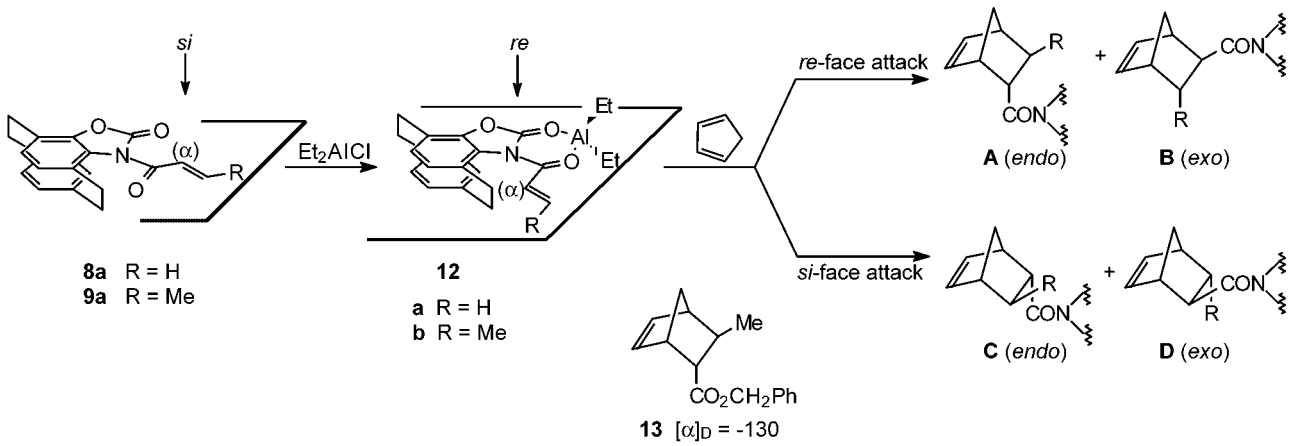


Table 1. Diels−Alder Reactions of Dienophiles 8 and 9 with Cyclopentadiene

entry	dienophile	catalyst	solvent	*T* (°C)	**A** (%)[a]	**B** (%)[a]	**C** (%)[a]	**D** (%)[a]	yield (%)[a]
1	**8**	Et_2AlCl	CH_2Cl_2	−100	86		14		70[b]
2	**9**	Et_2AlCl	CH_2Cl_2	−78	95.6	2.2	2.2		90[b]
3	**9**		CH_2Cl_2	rt	12.4		85.6	2.0	40[c]
4	**9**		H_2O	rt	8.3		89.3	2.4	42[c,d]
5	**9**	$InCl_3$	H_2O	rt	10.7		87.2	2.1	30[c]

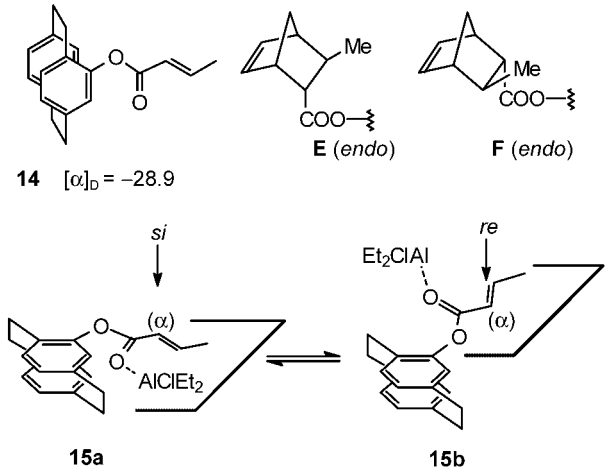
[a] Determined by ^{1}H NMR. [b] Yield of isolated main reaction adduct. [c] Conversion determined by ^{1}H NMR. [d] Yield of isolated **C** (R = Me) adduct 35%.

Section and Supporting Information) and by conversion of the cycloadduct **A** (R = Me) to the known benzyl ester **13**.[1d]

The stereochemical outcome of the $EtAlCl_2$-promoted Diels−Alder reactions is consistent with an endo addition of cyclopentadiene on the more accessible *re*-face[15] of the s-cis bidentate Lewis acid−dienophile complexes **12a**,**b** (Scheme 2), in agreement with literature data.[1b] The reversed endo face-selection observed in the cycloaddition of **9** carried out in the absence of the catalyst is due to the fact that the dienophile adopts the more stable s-cis conformation **9a** (Scheme 2) to minimize steric interactions of the olefin moiety with the C9−C10 ethylene bridge of [2.2]paracyclophane. As a consequence, the face of the dienophile exposed to the diene attack is reversed with respect to that of bidentate aluminum−dienophile complex **12b** (Scheme 2). The endo addition of cyclopentadiene again occurs on the less sterically hindered face of the dienophile, which in this case is the *si*-face, and consequently, the endo adduct **C** (R = Me) is the main reaction product (Table 1, entries 3 and 4). This hypothesis is supported by the Et_2AlCl-catalyzed cycloaddition of crotonate **14**, derived from **1**, with cyclopentadiene (Scheme 3). The reaction, which occurred at −20 °C (3 h, 90% yield), is highly endo-selective (endo/exo = 94:6), but face-unselective (**E**/**F** = 56:44) because the lack of a bidentate dienophile complex allows the cycloaddition to occur on the *si*-face and the *re*-face of **15a** and **15b**, respectively, which are conformations of comparable stability and that presumably give energetically comparable transition states.

Michael Reaction. Michael addition was accomplished using the Grignard reagent/cuprous bromide system in THF/Me_2S at −20 °C.[16] Under these conditions, the organometallic derived from bromobenzene, added to

Scheme 3



crotonyloxazolone **9**, afforded the Michael adduct **16** in 85% yield. The reaction is ≥ 99% *re*-face-selective.[15] The structure of **16** is supported by spectroscopic data (see Experimental Section and Supporting Information) and by its hydrolysis, which afforded the known acid **17** in 90% yield.[16,17] The chiral auxiliary **7** was recovered quantitatively and reused. The stereochemical

outcome of the reaction is again consistent with the conjugate addition of organometallic reagent to the less

(15) To facilitate the discussion of results, the *si*- and *re*-faces of carboxy and enolate imides are defined with respect to the unsaturated α-carbon of the CON group.

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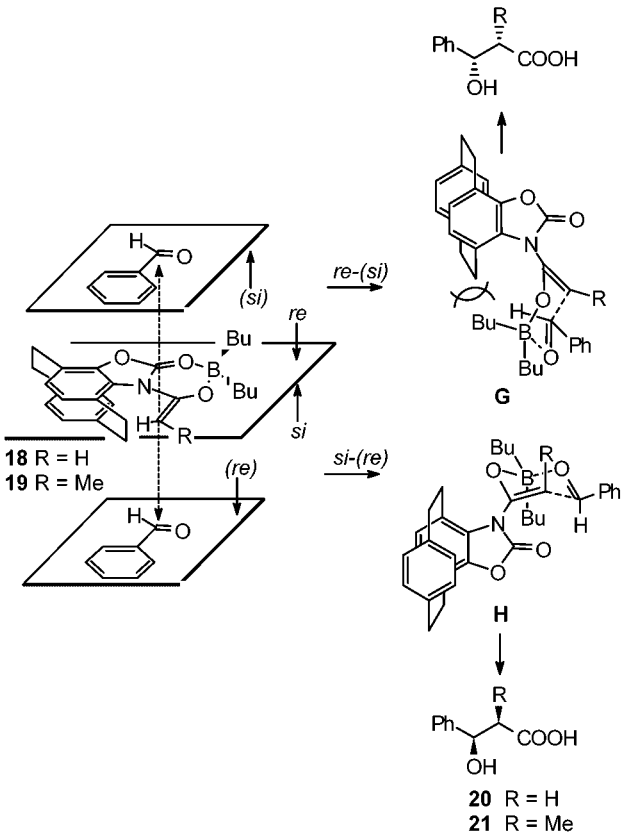
Scheme 4



sterically hindered *re*-face of **9**, which has the two carbonylic functionalities complexed by the metal cation and the crotonyl side-chain in the s-cis conformation likewise to aluminum complex **12b** depicted in Scheme 2.

Aldol Reactions. Oxazolones **10** and **11** and benzaldehyde were chosen to test the effectiveness of the chiral auxiliary in the aldol reaction.

Following standard procedures,[18] we first treated compounds **10** and **11**, obtained in nearly quantitative yields by N-acylation of lithium derivatives of **7** with acetyl and propionyl chloride, respectively, with Bu_2BOTf/Et_3N to give the boroenolates **18** and **19** (Scheme 4), which were allowed to react in situ with benzaldehyde at 0 °C. Oxidative workup allowed (+)-(*R*)-3-phenyl-3-hydroxypropionic acid (**20**) (ee 71%) and (+)-(2*R*,3*R*)-*syn*-2-methyl-3-phenyl-3-hydroxypropionic acid (**21**) (ee 90%; syn/anti = 80:20) in 70 and 75% yields, respectively, to be isolated. The cleavage of the auxiliary is quantitative, very easy, occurs in a completely exocyclic way, and does not require specific treatment. Once again, the removed oxazolone **7** can be reused. The configurations of the hydroxyacids **20** and **21** were proven by comparison with authentic specimens.[19] The boron enolates **18** and **19** react preferentially with their *si*-face[15] on the *re*-face of benzaldehyde, showing that the addition occurs with a reversed face-selectivity compared with the Diels−Alder and Michael additions. The Bu_2BOTf/Et_3N-supported aldol reaction is recognized to occur through the Zimmerman−Traxler pericyclic chairlike transition state[20] involving the metal (**G** and **H**, Scheme 4), while this does not occur in the Diels−Alder and Michael reactions for which a *metal-opened* transition state has been suggested.[21] This fact makes the transition states **H**,[22] coming from the attack of the *si*-face of complexes **18** and **19** on the *re*-face of benzaldehyde, less sterically crowded with respect to **G**, because the steric interactions of axial butyl group with the C9−C10 ethylene bridge of the paracyclophane moiety are reduced. The *si*-face diastereoselectivity is therefore preferred.

Conclusion

In conclusion, the (+)-(*R*)-[2.2]paracyclophane-[4.5-*d*]-1,3-oxazol-2(3*H*)-one **7**, the first known member of the oxazolone family with planar chirality, is an effective chiral auxiliary in asymmetric Diels−Alder and Michael reactions via α,*β*-unsaturated carboxy imides and in asymmetric aldol addition via enolate imide. The spatial relationship between the prochiral center and the C9−C10 ethylene bridge of the [2.2]paracyclophane moiety controls the diastereofacial selectivity so that the catalyzed Diels−Alder and Michael reactions occur prevalently on the *re*-face of the acceptor, whereas the aldol addition involves the *si*-face. Both enantiomers of the auxiliary are available and can be removed easily and quantitatively at the end of the asymmetric process.

Experimental Section

NMR spectra were recorded at 400 or 200 MHz for proton and at 100.6 or 50.3 MHz for carbon nuclei in $CDCl_3$ solution, if not otherwise specified. Optical rotations were measured at the sodium D line in $CHCl_3$ solution, if not otherwise specified, at room temperature. GC-MS analyses were carried out with 70 eV electron energy. GC analyses were performed with an SPB-5 fused silica capillary column (30 m, 0.25 mm diameter) on an "on column" injector system and an FID detector with hydrogen as the carrier gas. Column chromatography was carried out on silica gel 230−400 mesh. Reagents were purchased and used without further purification. Tetrahydrofuran and diethyl ether were dried using sodium metal and then distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Petroleum ether was the 35−60 °C boiling fraction. The organic solution obtained from workup of the reaction mixture was dried with sodium sulfate and concentrated under reduced pressure on a rotary evaporator with the water bath generally not exceeding 40 °C.

(+)-(*R*)-[2.2]Paracyclophano[4,5-*d*]-1,3-oxazol-2(3*H*)-one (7). Butyllithium (21.4 mL, 1.6 M in hexane, 34.2 mmol)

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(22) As suggested by a reviewer, the oxazolone ring should be oriented in the transition states as schematically depicted in **G** and **H** of Scheme 4. This reflects either the stereoelectronic requirement of amides and amines (the lone pair of nitrogen overlays the attached C=O or C=C bonds) or that the dipole interaction between the enolic oxygen and oxazolone carbonyl group is minimized. This allylic-like strain was observed by Evans for N-acyl oxazolidinone enolates.[18d] This interaction is present in the transition structures in which the enolic oxygen and the oxazolone carbonyl group preserve their starting cis relationship,[2] but this prevents the rotation of 180° about the exocyclic C−N bond (during the addition of benzaldehyde), because it is obstructed by the ethylene bridge of paracyclophane moiety. In any case, the relative stability of the transition state of **G** and **H** does not change.

was added dropwise to a solution of **2**[7a] (4.5 g, 16.8 mmol) in anhydrous diethyl ether (70 mL) containing TMEDA (5.1 mL, 34.0 mmol) and cooled at 0 °C under nitrogen and under stirring. The mixture was stirred at 0 °C for 1.5 h, and then *p*-tosyl azide (6.74 g, 34.2 mmol) in anhydrous diethyl ether (20 mL) was added dropwise. Stirring was continued for 4 h at 0 °C; the reaction was quenched with water and the mixture extracted with ethyl acetate. After the usual workup, the residue, roughly purified by flash chromatography, afforded crude **3** (ca. 5.5 g), which was reduced (0 °C for 15 min and 1 h at room temperature) by $LiAlH_4$ (0.25 g, 11.8 mmol) in anhydrous diethyl ether (70 mL) under stirring and under nitrogen. A 9:1 solution of THF/H_2O (10 mL) was then cautiously added under stirring to the mixture followed by ethyl chloroformate (4.5 mL, 47 mmol). After 1 h at room temperature, the mixture was filtered through Celite and the solid residue washed with ethyl acetate. The organic phase was washed with brine and worked up as usual to give crude **5** (ca. 5.5 g), which was solubilized in dioxane (60 mL). The mixture was acidified with concentrated HCl (2 mL) and stirred for 1 h at room temperature. Potassium carbonate (8 g) was cautiously added and the mixture refluxed for 1 h. After cooling, the mixture was filtered and the solid residue was washed with ethyl acetate. The organic phase, washed with brine and worked up as usual, gave crude **7**, which was purified by column chromatography eluting with petroleum ether/acetone 4:1 to give pure **7** (2.35 g, 50% total yield from **1**): mp 315 °C dec. (ethyl acetate); $[\alpha]_D$ +12.8 (*c* 1.0, DMSO); ^{1}H NMR (acetone-*d*) δ 2.65−2.88 (m, 2H), 2.90−3.05 (m, 4H), 3.10−3.27 (m, 2H), 6.42−6.66 (m, 6H); ^{13}C NMR (DMSO) δ 28.5, 29.6, 32.9, 33.3, 121.6, 123.5, 125.2, 125.4, 126.6, 128.8, 131.9, 132.4, 133.3, 137.8, 138.0, 143.2, 155.9; IR (KBr) ν 3450, 1760, 1425; MS *m*/*z* 265 (55), 161 (77), 133 (11) 104 (100), 78 (12). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.08; H, 5.69; N, 5.23.

(−)-(*R*)-3-(2-Propenoyl)-[2.2]paracyclophano[4,5-*d*]-1,3-oxazol-2(3*H*)-one (8). A 3 M diethyl ether solution of MeMgBr (1.27 mL, 3.8 mmol) was added to a stirred solution of **7** (0.5 g, 1.9 mmol) in anhydrous THF cooled to 0 °C. The mixture was stirred for 30 min at 0 °C, and then a solution of acryloyl chloride (0.31 mL, 3.8 mmol) in anhydrous THF (2 mL) at −78 °C was added. The mixture was stirred at −78 °C for 10 min and at 0 °C for 20 min; the reaction was quenched with saturated aqueous ammonium chloride, and then the mixture was extracted with ethyl acetate. Usual workup and column chromatography purification (eluent *n*-hexane/ethyl acetate 9:1) afforded pure **8** (0.56 g, yield 93%): mp 159−161 °C (hexane/ethyl acetate); $[\alpha]_D$ −269.2 (*c* 0.60, $CHCl_3$); ^{1}H NMR δ 2.31 (dt, 1H, *J* = 13.4, 8.9 Hz), 2.65−3.35 (m, 6H,), 3.38 (ddd, 1H, *J* = 13.9, 9.0, 1.0 Hz), 6.14 (dd, 1H, *J* = 10.4, 1.5 Hz), 6.40−6.72 (m, 6H), 6.78 (dd, 1H, *J* = 16.9, 1.5 Hz), 7.56 (dd, 1H, *J* = 16.9, 10.4 Hz). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.30; H, 5.35; N, 4.40.

(−)-(*R*)-3-((*E*)-2-Butenoyl)-[2.2]paracyclophano[4,5-*d*]-1,3-oxazol-2(3*H*)-one (9). Butyllithium (1.6 M in *n*-hexane, 2.4 mL, 3.8 mmol) was added to a stirred solution of **7** (0.5 g, 1.9 mmol) in anhydrous THF cooled to 0 °C. The mixture was stirred for 20 min at 0 °C, and then a solution of (*E*)-crotonyl chloride (0.36 mL, 3.8 mmol) in anhydrous THF (2 mL) was added. The stirring was continued for 1 h at 0 °C. The mixture, quenched with saturated aqueous ammonium chloride and worked up as described above for **8**, gave pure **9** (0.59 g, yield 94%): mp 186−188 °C (hexane/ethyl acetate); $[\alpha]_D$ −267.4 (*c* 0.54, $CHCl_3$); ^{1}H NMR δ 2.11 (dd, 3H, *J* = 6.4, 1.0 Hz), 2.32 (dt, 1H, *J* = 13.4, 9.0 Hz), 2.60−3.45 (m, 7H), 6.40−6.75 (m, 6H), 7.27 (dq, 1H, *J* = 15.2, 1.0 Hz), 7.43 (dq, 1H, *J* = 15.2, 6.4 Hz). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.72; H, 5.71; N, 4.22.

(−)-(*R*)-3-Acyl-[2.2]paracyclophano[4,5-*d*]-1,3-oxazol-2(3*H*)-one (10): prepared as described for **9** with acyl chloride and purified by column chromatography eluting with *n*-hexane/ethyl acetate 8:2; yield 95%; mp 206−208 °C (*n*-hexane/ethyl acetate); $[\alpha]_D$ −175.0 (*c* 0.54, $CHCl_3$); ^{1}H NMR δ 2.34 (dt, 1H, *J* = 13.4, 8.9 Hz), 2.65−3.35 (m, 6H), 2.84 (s, 3H), 3.45 (ddd, 1H, *J* = 13.8, 8.9, 0.8 Hz), 6.37−6.72 (m, 6H). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.20; H, 5.60; N, 4.59.

(−)-(*R*)-3-Propionyl-[2.2]paracyclophano[4,5-*d*]-1,3-oxazol-2(3*H*)-one (11): prepared as described for **9** with propionyl chloride and purified by column chromatography eluting with *n*-hexane/ethyl acetate 8:2; yield 95%; mp 195−196 °C (*n*-hexane/ethyl acetate); $[\alpha]_D$ −181.1 (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 1.39 (t, 3H, *J* = 7.3 Hz), 2.31 (dt, 1H, *J* = 13.4, 9.0 Hz), 2.65−3.42 (m, 8H), 3.45 (ddd, 1H, *J* = 13.8, 9.1, 1.0 Hz), 6.35−6.75 (m, 6H). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.86; H, 5.98; N, 4.32.

(−)-(*R*)-4-((*E*)-2-Butenoyl)-oxy[2.2]paracyclophane (14): Prepared as described for **9** with (+)-(*R*)-4-hydroxy[2.2]-paracyclophane and (*E*)-crotonyl chloride and purified by column chromatography eluting with *n*-hexane/ethyl acetate 95:5; yield 95%; mp 133−135 °C (*n*-hexane/ethyl acetate); $[\alpha]_D$ −28.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 2.02 (dd, 3H, *J* = 6.9, 1.7 Hz), 2.69 (m, 1H), 2.90−3.20 (m, 7H), 6.04 (d, 1H, *J* = 1.6 Hz), 6.11 (dq, 1H, *J* = 15.5, 1.7 Hz), 6.40−6.57 (m, 5H), 6.91 (dd, 1H, *J* = 7.8, 1.9 Hz), 7.24 (dq, 1H, *J* = 15.5, 6.9 Hz). Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 82.26; H, 6.91.

(−)-(*R*)-3-[(1′*S*,2′*S*,4′*S*)-Bicyclo[2.2.1]hept-5′-en-2′-ylcarbonyl]-[2.2]paracyclophano[4,5-*d*]-1,3-oxazol-2(3*H*)-one (A, R = H). Diethylaluminum chloride (1.8 M in toluene, 0.12 mL, 0.21 mmol, 1.4 equiv) was first added to a stirred solution of acrylate imide **8** (48 mg, 0.15 mmol) in anhydrous dichloromethane (3 mL) cooled to −100 °C, and then precooled cyclopentadiene (0.6 mL, 7.4 mmol, 50 equiv) was added. After 10 min, the mixture was poured in 1 M HCl (10 mL), extracted with dichloromethane, and worked up as usual. ^{1}H NMR analyses revealed the presence of **A** (R = H) and **C** (R = H) in an 86:14 ratio. Column chromatography, eluting with petroleum ether/diethyl ether 95:5, and recrystallization afforded the major compound **A** as a crystalline solid (70% yield): mp 203−205 °C (*n*-hexane/ethyl acetate); $[\alpha]_D$ − 233.7 (*c* 0.46, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.59 (d broad, 1H, *J* = 8.3 Hz), 1.63 (dq, 1H, *J* = 8.3, 1.8 Hz), 1.71 (ddd, 1H, *J* = 11.8, 4.4, 2.4 Hz), 1.98 (ddd, 1H, *J* = 11.8, 8.8, 3.7 Hz), 2.54 (ddd, 1H, *J* = 13.3, 9.6, 7.6 Hz), 2.70−3.40 (m, 8H), 3.66 (s broad, 1H), 4.36 (ddd, 1H, *J* = 8.3, 4.2, 4.0 Hz), 6.12 (dd, 1H, *J* = 5.7, 2.7 Hz), 6.45 (dd, 1H, *J* = 5.7, 3.1 Hz), 6.46−6.60 (m, 5H), 6.70 (dd, 1H, *J* = 7.9, 1.7 Hz); ^{13}C NMR (400 MHz) δ 28.60, 28.63, 33.57, 33.64, 34.62, 43.09, 44.20, 47.60, 51.05, 122.16, 125.82, 126.31, 127.10, 130.27, 131.14, 131.33, 131.47, 132.23, 132.95, 138.23, 138.79, 139.54, 142.72, 151.82, 171.67. Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 78.12; H, 6.07; N, 3.58.

(−)-(*R*)-3-[((1′*S*,2′*S*,3′*R*,4′*R*)-3′-Methylbicyclo[2.2.1]hept-5′en-2′-yl)carbonyl]-[2.2]paracyclophano[4,5-*d*]-1,3-oxazol-2(3*H*)-one (A, R = Me). Diethylaluminum chloride (1.8 M in toluene, 0.12 mL, 0.21 mmol, 1.4 equiv) was added to a stirred solution of crotonate imide **9** (50 mg, 0.15 mmol) and cyclopentadiene (0.3 mL, 3.7 mmol, 25 equiv) in anhydrous dichloromethane (0.3 mL) cooled to −78 °C. After stirring for 5 min at −78 °C, the mixture was poured in 1 M HCl (10 mL), extracted with dichloromethane, and worked up as usual. ^{1}H NMR analyses revealed the presence of three isomers in a 95.6:2.2:2.2 ratio. Column chromatography eluting with petroleum ether/diethyl ether 95:5 and recrystallization afforded the title compound as a crystalline solid (90% yield): mp 176−178 °C (*n*-hexane/ethyl acetate); $[\alpha]_D$ − 244.0 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.20 (d, 3H, *J* = 7.0 Hz), 1.65 (dq, 1H, *J* = 8.6, 1.7 Hz), 1.89 (d broad, 1H, *J* = 8.6), 2.26 (m, 1H), 2.51 (ddd, 1H, *J* = 13.3, 9.6, 7.7 Hz), 2.64 (s broad, 1H), 2.70−3.35 (m, 7H), 3.63 (s broad, 1H), 3.86 (dd, 1H, *J* = 4.5, 3.4 Hz), 6.11 (dd, 1H, *J* = 5.7, 2.7 Hz), 6.45−6.60 (m, 6H), 6.70 (dd, 1H, *J* = 7.9, 1.8 Hz): ^{13}C NMR (400 MHz) δ 20.40, 28.59, 30.51, 33.66, 34.64, 36.19, 47.82, 48.24, 49.47, 53.01, 122.17, 125.79, 126.30, 127.08, 130.46, 131.12, 131.31, 131.48, 132.22, 132.96, 138.21, 138.78, 140.90, 142.73, 151.82, 171.43. Anal. Calcd for $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51. Found: C, 78.29; H, 6.33; N, 3.49.

Removal of Chiral Auxiliary. (−)-Benzyl-(1*S*,2*S*,3*R*,4*R*)-3-Methylbicyclo[2.2.1]hept-5-ene-2-carboxilate (13). Butyllithium (1.6 M in *n*-hexane, 0.125 mL, 0.2 mmol) was added

to a stirred solution of benzyl alcohol (0.31 mL, 0.3 mmol) in anhydrous THF (1 mL) cooled at −78 °C. A solution of the adduct **A** (R = Me) (39.9 mg, 0.1 mmol) in anhydrous THF (1 mL) was added and the mixture warmed to 0 °C. The solution was stirred at this temperature for 3 h and the reaction quenched with saturated aqueous ammonium chloride. The mixture was concentrated in vacuo, diluted with water, and extracted with dichloromethane. After the usual workup, the residue was purified by column chromatography eluting with petroleum ether/diethyl ether 9:1 to give **13**[1d] (20 mg, 82% yield), $[\alpha]_D$ −130 (*c* 0.5, $CHCl_3$), and the chiral auxiliary **7** (24 mg, 91%).

(+)-(*R*)-3-[((1′*R*,2′*R*,3′*S*,4′*S*)-3′-Methylbicyclo[2.2.1]hept-5′-en-2′-yl)carbonyl]-[2.2]paracyclophano[4,5-*d*]-1,3-oxazol-2(3*H*)-one (C, R = Me). Cyclopentadiene (0.3 mL, 3.7 mmol, 25 equiv) was added to a stirred suspension of crotonate imide **9** (50 mg, 0.15 mmol) in H_2O (1 mL). After stirring at room temperature for 30 h, the mixture was extracted with dichloromethane and worked up as usual. ^{1}H NMR analyses revealed the presence of three isomers in an 89.3:8.3:2.4 ratio. Column chromatography eluting with petroleum ether/diethyl ether 95:5 and recrystallization afforded the title compound as a crystalline solid (35% yield): mp 197−198 °C (hexane/ethyl acetate); $[\alpha]_D$ +13.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.30 (d, 3H, *J* = 7.0 Hz), 1.57 (dq, 1H, *J* = 8.7, 1.6 Hz), 1.80 (d broad, 1H, *J* = 8.7), 2.15 (m, 1H), 2.25 (ddd, 1H, *J* = 13.6, 9.0 Hz), 2.65 (s broad, 1H), 2.65−3.35 (m, 7H), 3.46 (s broad, 1H), 3.77 (dd, 1H, *J* = 4.7, 3.1 Hz), 5.95 (dd, 1H, *J* = 5.6, 2.8 Hz), 6.40−6.60 (m, 6H), 6.68 (dd, 1H, *J* = 8.0, 1.6 Hz); ^{13}C NMR (400 MHz) δ 21.16, 28.28, 33.18, 33.61, 34.91, 41.47, 47.01, 47.09, 49.99, 53.03, 122.26, 125.51, 126.02, 127.04, 130.45, 130.52, 131.77, 131.80, 132.25, 132.89, 138.02, 138.37, 138.94, 142.52, 151.88, 172.48. Anal. Calcd for $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51. Found: C, 78.29; H, 6.33; N, 3.49.

(−)-(*R*)-3-(3-Phenylbutanoyl)-[2.2]paracyclophano[4,5-*d*]-1,3-oxazol-2(3*H*)-one (16). A 1 M solution of phenylmagnesium bromide in THF (3 mL, 3 mmol) was added to a stirred solution of CuBr·SMe_2 (0.304 g, 1.5 mmol) in anhydrous THF (3.5 mL) and SMe_2 (1.75 mL) cooled at −40 °C. After 15 min, a solution of **9** (0.333 g, 1 mmol) in anhydrous THF (3 mL) was added dropwise, over a period of 20 min, to the organocopper solution cooled at −20 °C and the resulting mixture was stirred at this temperature for 30 min. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. Workup as usual and column chromatography eluting with petroleum ether/diethyl ether 95:5 afforded **16** as a crystalline solid (0.35 g, 85% yield): mp 165−167 °C (hexane/ethyl acetate); $[\alpha]_D$ −88.3 (*c* 0.58, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.32 (ddd, 1H, *J* = 13.4, 10.0, 8.3 Hz), 1.46 (d, 3H, *J* = 7.0), 2.46−2.65 (m, 2H), 2.71 (ddd, 1H, *J* = 13.4, 10.5, 4.2 Hz), 2.85−3.10 (m, 3H), 3.23 (ddd, 1H, *J* = 13.4, 10.3, 4.0 Hz), 3.34 (dd, 1H, *J* = 17.2, 4.8 Hz), 3.61 (m, 1H), 3.74 (dd, 1H, *J* = 17.2, 9.6 Hz), 6.07 (dd, 1H, *J* = 8.0, 1.5 Hz), 6.35−6.62 (m, 5H), 7.20−7.50 (m, 5H); ^{13}C NMR (400 MHz) δ 22.60, 28.37, 32.21, 33.58, 34.76, 36.03, 45.41, 122.26, 125.51, 125.90, 126.53, 128.82, 127.26, 128.69, 130.75, 130.94, 131.71, 131.81, 132.74, 138.22, 138.29, 142.55, 145.67, 151.76, 168.95. Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.81; H, 6.12; N, 3.40. Found: C, 78.97; H, 6.09; N, 3.42.

Removal of Chiral Auxiliary. (+)-(*S*)-3-Phenylbutanoic Acids (17). H_2O_2 (30%, 0.045 mL) was added to a solution of **16** (41 mg, 0.1 mmol) in an 8:2 solution THF/H_2O (1.25 mL) cooled to −5 °C. A 0.8 M aqueous solution of LiOH (0.2 mL, 0.16 mmol) was then added dropwise keeping the temperature below 0 °C. The mixture was stirred at 0 °C for 1 h, and then a 1.3 M solution of Na_2SO_3 (0.3 mL) was added. The organic solvent was evaporated, and the aqueous mixture was extracted with ethyl acetate. The organic phase was worked up as usual to give the chiral auxiliary **7** (24 mg, 90%). The mother liquor was acidified with concentrated HCl to pH 1−2 and extracted with ethyl acetate. The usual workup gave **17**[16] (15 mg, 90% yield), $[\alpha]_D$ +54.0 (*c* 0.5, benzene).

Aldol Reaction. Hydroxyacids 20 and 21. Triethylamine (0.42 mL, 3 mmol) followed by dibutylboron triflate (1 M in CH_2Cl_2, 2.5 mmol) was added to a solution of acyloxazolone (**10** or **11**, 2 mmol) in anhydrous dichloromethane (10 mL) cooled to −78 °C. The reaction mixture was allowed to warm to 0 °C, and after 1 h, the solution was cooled again to −78 °C and benzaldehyde (3 mmol) in dichloromethane (2 mL) was added. After 30 min at −78 °C and 3 h at 0 °C, the reaction was quenched with pH 7.0 phosphate buffer (0.1 M, 10 mL), methanol (10 mL), and a 1:1 solution of 30% H_2O_2/MeOH (10 mL). After 1 h at 0 °C, the mixture was concentrated in vacuo, and the residue, diluted with saturated aqueous $NaHCO_3$ (10 mL), was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated in vacuo and afforded the chiral auxiliary **7** (90% yield). The aqueous phase, acidified with concentrated HCl and worked up as usual, allowed (+)-(*R*)-3-phenyl-3-hydroxypropionic acid **20**[19] (ee 71%) and (+)-(2*R*,3*R*)-*syn*-2-methyl-3-phenyl-3-hydroxypropionic acid **21**[19] (ee 90%; syn/anti 80:20) in 70 and 75% yields, respectively, to be isolated.

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Supporting Information Available: ^{1}H and ^{13}C NMR peak assignment, $[\alpha]_D$, and MS *m/z* of compounds **2**−**11**, **14**, **A** (R = H), **C** (R = H), **A** (R = Me), **C** (R = Me), and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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