Applications of Intramolecular Cyclopropanations of Chiral Secondary Allylic Diazoacetates

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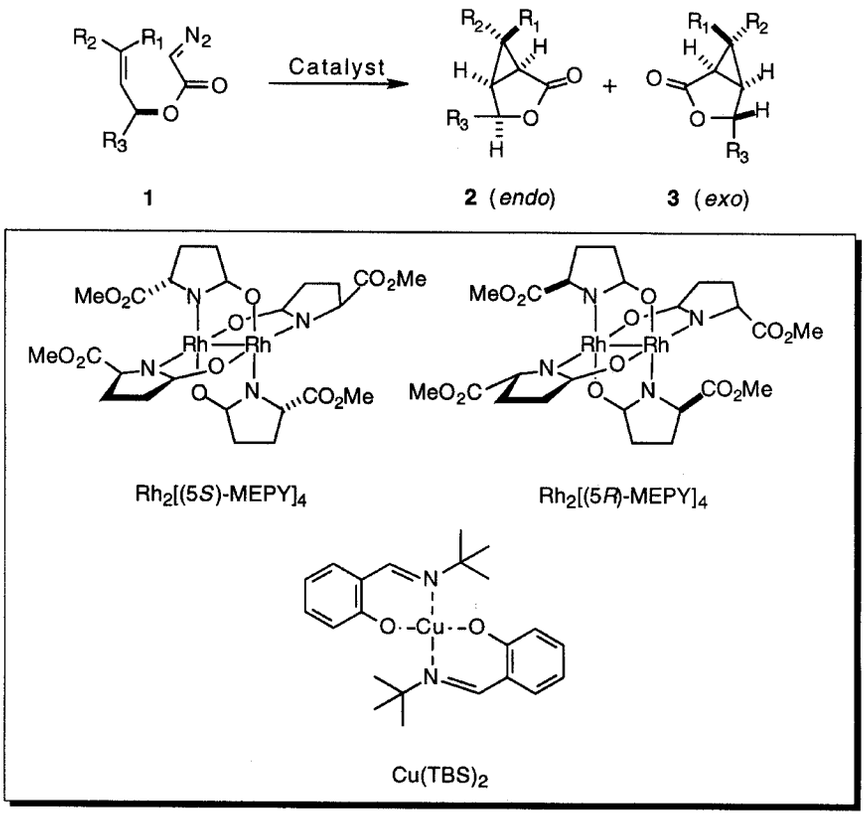
The diastereomeric secondary allylic diazoacetates **6a,b** and **8a,b**, which were readily prepared from the common intermediate **4**, were cyclized in the presence of the achiral catalyst $Cu(TBS)_2$ to furnish mixtures of the adducts **9a,b/10a,b** and **12a,b/13a,b**, respectively; in these cyclizations, the diastereoselectivity of the reaction was substrate controlled. When **6a,b** and **8a,b** were cyclized in the presence of the chiral catalysts $Rh_2[(5S)\text{-MEPY}]_4$ or $Rh_2[(5R)\text{-MEPY}]_4$, the substrate-based selectivity could be reversed if the chirality of the substrate and catalyst were matched. The advantages associated with the use of chiral catalysts to effect the diastereoselective cyclization of chiral allylic diazoacetates were demonstrated by the synthesis of **25**, which comprises the cyclopropane subunit found in the diterpene ingol B (**14**).

INTRODUCTION

Cyclopropane rings are not only essential components of natural products and other compounds having biological importance, but they are also useful synthetic intermediates. Consequently, there have been numerous investigations directed toward the design and development of methods for the asymmetric and diastereoselective syntheses of substituted

Scheme I



Dedicated to the memory of Ta-shue Chou (1950-1999), my first Ph. D. student, a scholar, a teacher, and a friend.

cyclopropanes. One tactic that has proven very useful involves the intramolecular cyclopropanation of primary allylic diazoacetates of the general type **1** (R_3 = H) in the presence of chiral catalysts such as Rh_2[(5*S*)-MEPY]$_4$ or Rh_2[(5*R*)-MEPY]$_4$ to furnish the *endo* adducts **2** (Scheme I).[1] These cyclizations typically proceeded with high levels of enantioselectivity, especially with *Z*-disubstituted olefins. We have demonstrated the efficacy of these enantioselective, intramolecular cyclopropanations by exploiting them as key steps in the syntheses of a novel class of conformationally-constrained peptide mimics that have been incorporated in biologically active pseudopeptides.[2]

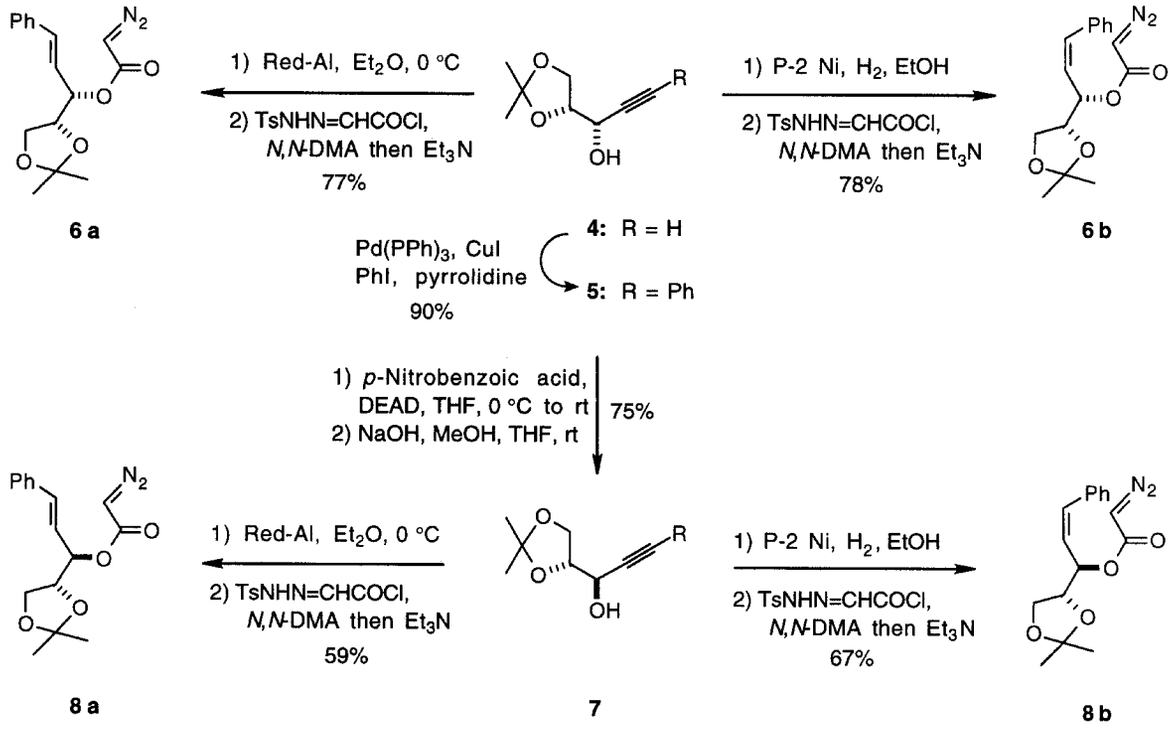
In order to extend the utility of asymmetric cyclopropanations in organic synthesis, we became intrigued with the behavior of chiral secondary allylic diazoacetates within this reaction manifold. Indeed, we discovered that when diazoacetates derived from secondary allylic alcohols (**1**, R_3 = alkyl) were cyclized using the appropriately matched chiral rhodium catalyst, the *endo* adducts **2** were again formed as the major products, usually with excellent diastereoselectivity.[3] On the other hand, cyclizations of (**1**, R_3 = alkyl) in the presence of the achiral catalyst $Cu(TBS)_2$ typically afforded the *exo* adducts **3** with good to excellent diastereoselectivity; cyclizations of *Z*-disubstituted olefins were more stereoselective than those of the corresponding *E*-alkenes. Moreover, in these reactions the presence of a stereogenic center in the appended alkyl group R_3 did not have a significant effect upon the stereochemical outcome of the reaction. Rather the primary stereochemical determinant was the relationship between the configurations at the stereogenic center in the catalyst and at the allylic center in the diazoacetate **1** (R_3 = alkyl). In this account, we provide the details of some diastereoselective cyclizations of secondary allylic diazoacetates **1** in which R_3 contains a protected diol array.[3c] We also present the application of this methodology to the enantioselective synthesis of a key structural subunit in the novel diterpene ingol B.

RESULTS AND DISCUSSION

Development of the Methodology

The synthesis of the secondary allylic diazoacetates **6a,b** and **8a,b** required for this investigation commenced with the known propargyl alcohol **4**, which was available in three steps and good overall yield from D-arabitol (Scheme II).[4] Arylation at the alkyne with iodobenzene in the presence of catalytic $Pd(PPh_3)_4$ and CuI in pyrrolidine gave **5** (90%).[5] The epimeric alcohol **7** was prepared from **5** in 75% yield using a variant of the Mitsunobu reaction that was recently developed in our laboratories.[6] Stereoselective reduction of **5** by the action of either Red-Al[7] or P-2 Ni[8] gave the (*E*)- or (*Z*)-alkenes

Scheme II



respectively, and these alkenes were then transformed into the corresponding *erythro* allylic diazoacetates **6a,b** in good overall yields (77-78%).[9] The epimeric alcohol **7** was transformed into the *threo*-allylic diazoacetates **8a,b** in a similar fashion, albeit in slightly lower yields (59% and 67%, respectively).

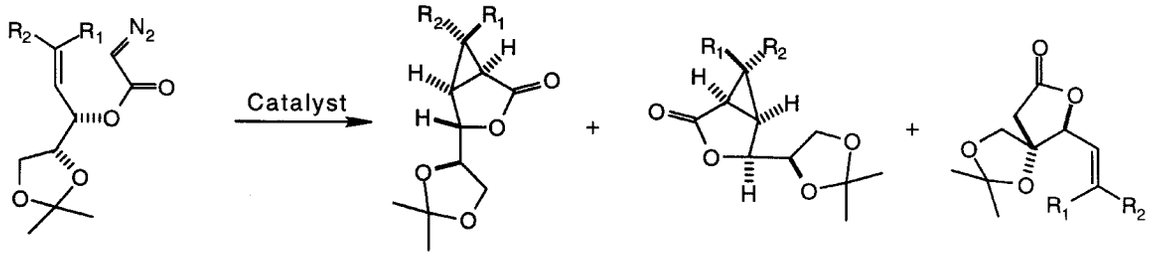
When the *erythro* allylic diazoesters **6a,b** were heated in the presence of catalytic amounts of $Cu(TBS)_2$, $Rh_2[5(S)\text{-MEPY}]_4$ and $Rh_2[5(R)\text{-MEPY}]_4$, mixtures of the *exo* adducts **9a,b** and the *endo* adducts **10a,b** were produced (Table 1). In addition to the expected cyclopropanes, the lactones **11a,b** were also formed during the thermal decompositions of **6a,b** in the presence of $Rh_2[5(S)\text{-MEPY}]_4$. Although **11a** was a minor product (30% yield) from the reaction of **6a**, lactone **11b** was the major product (72% yield) from the cyclization of **6b**. These lactones were presumably formed because of a stereochemical "mismatch" between the chiral substrate and the chiral rhodium catalyst that resulted in significant steric interactions in transition states leading to cyclopropanation. Consequently, the putative metallocarbene intermediate inserts into the carbinol C-H bond rather than cyclopropanating the carbon-carbon double bond; such C–H insertions have been previously observed.[11]

In a similar fashion, the thermolysis of the diastereomeric *threo* diazoacetates **8a,b** in the presence of the same catalysts furnished mixtures of the *exo* adducts **12a,b** and the *endo* adducts **13a,b**,and these results are summarized in Table 2.[10] In these cyclizations, stereochemical mismatches between substrate and catalyst were not sufficiently large as to result in the formation of isolable quantities of lactones arising from C–H insertion. The basis for the difference in chemical reactivity for **8a,b** compared to that of **6a,b**, which did undergo C–H insertion in the presence of $Rh_2[5(S)\text{-MEPY}]_4$, is unknown.

The data presented in Tables 1 and 2 reveal a number of trends concerning the cyclopropanations of **6a,b** and **8a,b**. When $Cu(TBS)_2$ was employed, the *exo* diastereomer was favored in all cases, suggesting that neither the geometry of the carbon-carbon double bond nor the relative stereochemical relationship between the two adjacent stereogenic centers greatly affects the stereochemical course of the reaction. Rather it appears that there is a conformational bias for the intermediate metallocarbene that determines the stereochemistry of the addition, and examination of models for the two possible transition states for the cyclization of **6a** and **6b** reveal some useful insights (Scheme III). In particular, there is a steric interaction ($A^{1,3}$-strain) that develops between the olefin and the acetonide in the *endo* transition state. Because this allylic strain is absent in the *exo* transition state, the *exo* adducts are formed preferentially. Similar transition states may be envisioned for the cyclizations of **8a,b**.

The cyclizations of **6a,b** and **8a,b** in the presence of the chiral catalysts $Rh_2[(5R)\text{-MEPY}]_4$ and $Rh_2[(5S)\text{-MEPY}]_4$ are governed both by steric interactions within the substrate (i.e.,

Table 1. The Intramolecular Cyclopropanations of **6a,b**



6a: R_1 = H, R_2 = Ph
6b: R_1 = Ph, R_2 = H

9a: R_1 = H, R_2 = Ph
9b: R_1 = Ph, R_2 = H

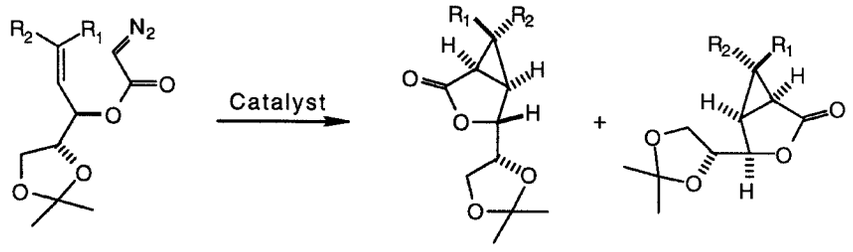
10a: R_1 = H, R_2 = Ph
10b: R_1 = Ph, R_2 = H

11a: R_1 = H, R_2 = Ph
11b: R_1 = Ph, R_2 = H

Substrate	Catalyst	*exo*	*endo*	Combined Yield (%)	Yield (%) of **11**
	$Cu(TBS)_2$	4	1	43	a
6a	$Rh_2[(5S)\text{-MEPY}]_4$	2	1	64	30
	$Rh_2[(5R)\text{-MEPY}]_4$	1	4	87	a
	$Cu(TBS)_2$	4	1	45	a
6b	$Rh_2[(5S)\text{-MEPY}]_4$	1	a	2	72
	$Rh_2[(5R)\text{-MEPY}]_4$	1	10	70	a

[a] Not isolated

Table 2. The Intramolecular Cyclopropanations of **8a,b**



8a: R_1 = H, R_2 = Ph
8b: R_1 = Ph, R_2 = H

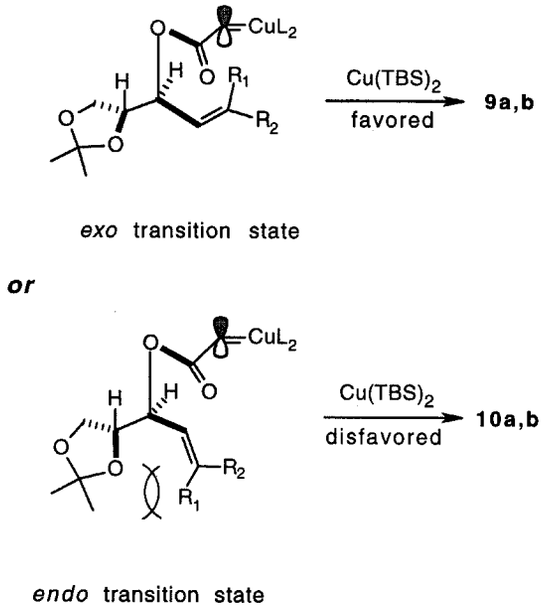
12a: R_1 = H, R_2 = Ph
12b: R_1 = Ph, R_2 = H

13a: R_1 = H, R_2 = Ph
13b: R_1 = Ph, R_2 = H

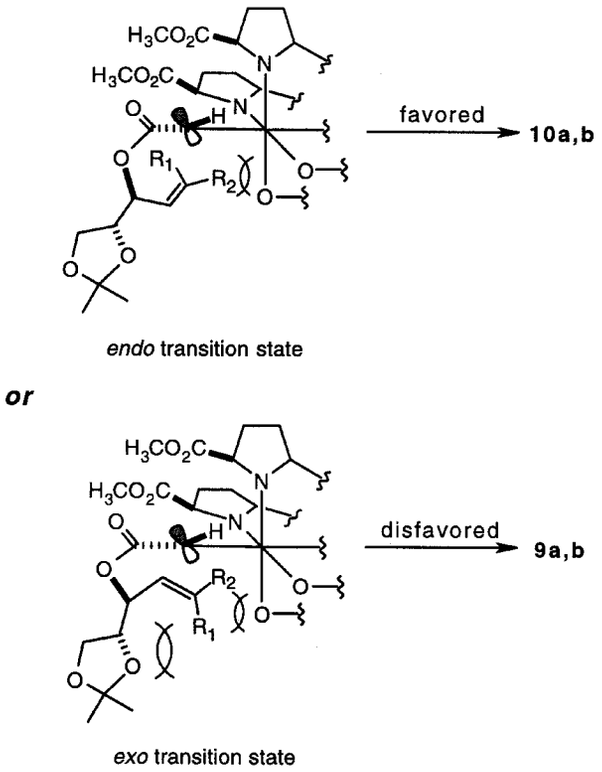
Substrate	Catalyst	*exo*	*endo*	Combined Yield, %
	$Cu(TBS)_2$	5	1	89
8a	Rh_2[(5*S*)-MEPY]$_4$	1	3	83
	Rh_2[(5*R*)-MEPY]$_4$	2	1	66
	$Cu(TBS)_2$	5	1	64
8b	Rh_2[(5*S*)-MEPY]$_4$	1	20	56
	Rh_2[(5*R*)-MEPY]$_4$	1.5	1	69

substrate control as shown in Scheme III) and by interactions that arise from the stereochemical relationship between the catalyst and the substrate (i.e., catalyst or reagent control).[3a] For example, the interactions between the chiral catalyst Rh_2[(5*R*)-MEPY]$_4$ and the allylic stereocenter in the diazoacetates **6a,b** are "matched" as are the interactions between Rh_2[(5*S*)-MEPY]$_4$ and **8a,b**. "Mismatched" interactions occur when the enantiomeric rhodium catalysts were employed for these substrates. These interactions may be visualized by considering the possible transition states for the cyclizations of **6a,b** catalyzed by Rh_2[(5*R*)-MEPY]$_4$ (Scheme IV) and by Rh_2[(5*S*)-MEPY]$_4$ (Scheme V). Thus, in the transition state for the cyclization of **6a** (R_1 = H, and R_2 = Ph), the *endo* product **10a** is only modestly favored (4:1) because the

Scheme III



Scheme IV



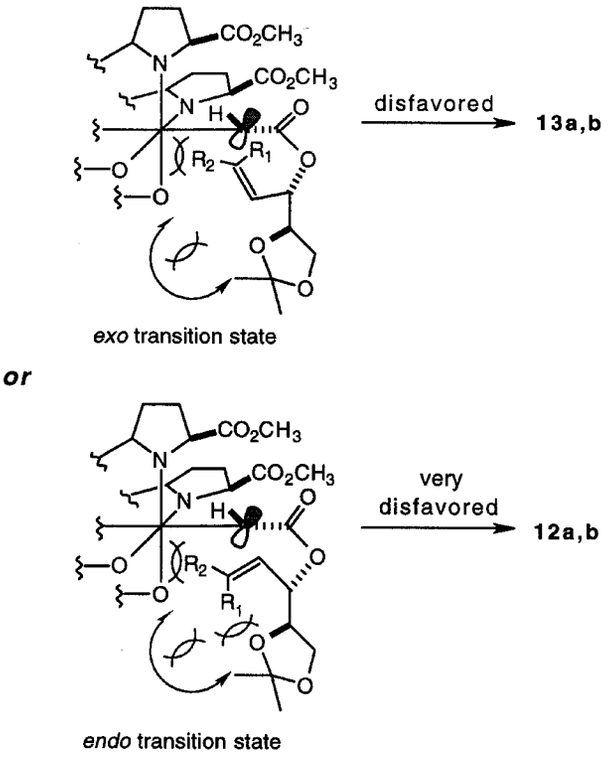
olefinic phenyl substituent (R_2) is directed into the face of the catalyst in both proposed transition states. In the *exo* transition state, not only is there a similar interaction between the olefinic terminus and the catalyst, but there is also a steric interaction that develops between the olefin and the acetonide. In the analogous transition states for the cyclization of **6b** (R_1 = Ph, and R_2 = H), the *endo* transition state is more highly favored (10:1) since there are no major steric interactions between the substrate and the catalyst. Indeed, we have generally found that the intramolecular cyclopropanations of (*E*)-disubstituted olefinic substrates catalyzed by chiral rhodium catalysts were less selective than those of the corresponding (*Z*)-disubstituted substrates.

When **6a** or **6b** is decomposed in the presence of Rh_2[(5*S*)-MEPY]$_4$, C–H insertion was found to be a significant side reaction for **6a** and the dominant reaction pathway for **6b**. Examination of the two possible transition states for the intramolecular cyclopropanations of **6a** and **6b** reveals a number of unfavorable steric interactions are readily apparent in each (Scheme V). In both transition states, both the olefin and the pendant acetonide must be brought into close proximity with the face of the catalyst. Furthermore, the *endo* transition state is further disadvantaged by the presence of allylic strain between the pendant acetonide and the olefin. The combination of these interactions leads to a sterically congested environment, making cyclopropanation an energetically less favorable reaction relative to C–H insertion. It is interesting to note that the diastereomeric *threo* diazoacetates **8a,b** did not exhibit the same tendency toward C–H insertion in the mismatched substrate/catalyst pair.

Application of Diastereoselective Cyclopropanations

Once the general trends of the intramolecular cyclopropanation reactions of *erythro* and *threo* secondary allylic diazoacetates were known, we sought to apply this methodology to a practical problem in total synthesis, and ingol B (**14**) was identified as a suitable target (Scheme VI). This cyclopropane-containing natural product, which is a member of the tumor promoting class of diterpenes known as the ingenanes, was isolated from the latex of *E. canariensis* of the genus *Euphorbia*.[12] Ingol B contains a dimethylcyclopropane subunit as an integral part of its skeleton that also includes a tetrasubstituted epoxide, a trisubstituted olefin, a *syn* 1,2-diol, and a total of ten stereocenters.[13] Although **14** does not exhibit the same tumor promoting ability that has been observed for other members of this class of natural products,[12a] it participates in both the protein kinase C and the Ca^{+2}-calmodulin pathways.[14] There has been no synthesis of **14** to date, and we

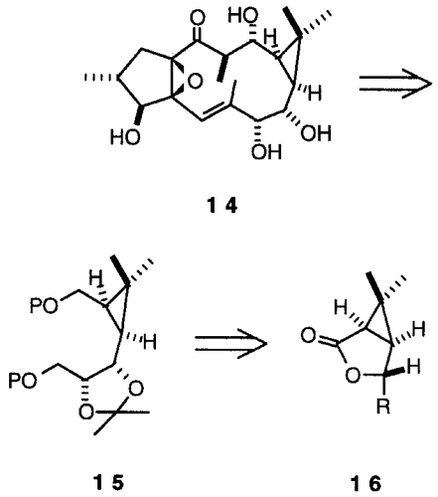
Scheme V



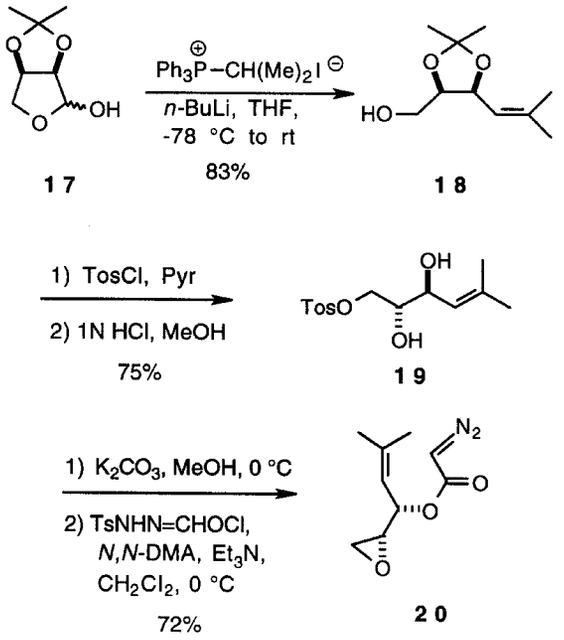
envisioned that it could be derived from the highly oxygenated right-hand fragment **15**, which was identified as the initial subgoal of our approach. This substituted cyclopropane **15** would then in turn be elaborated from the dimethylcyclopropyl lactone **16**, wherein R is either a diol or oxirane moiety. We describe herein the application of a diastereoselective intramolecular cyclopropanation reaction to prepare **16**.

The synthesis of a substituted lactone **16** wherein R is an epoxide commenced with isopropylidene-D-ribono-lactol **17**, which was subjected to a Wittig olefination with isopropylidene triphenylphosphorane to give **18** in 83% yield (Scheme VII).[15] Following conversion of the primary hydroxyl group to a tosylate, the acetal protecting group was removed by the action of 1 N HCl in MeOH to give **19** in 75% overall yield.[16] Treatment of **19** with K_2CO_3 in degassed

Scheme VI



Scheme VII



MeOH at 0 °C furnished an intermediate allylic alcohol that was converted according to the Corey-Myers protocol[9] into the epoxy allylic diazoacetate **20** in 72% yield from **19**.

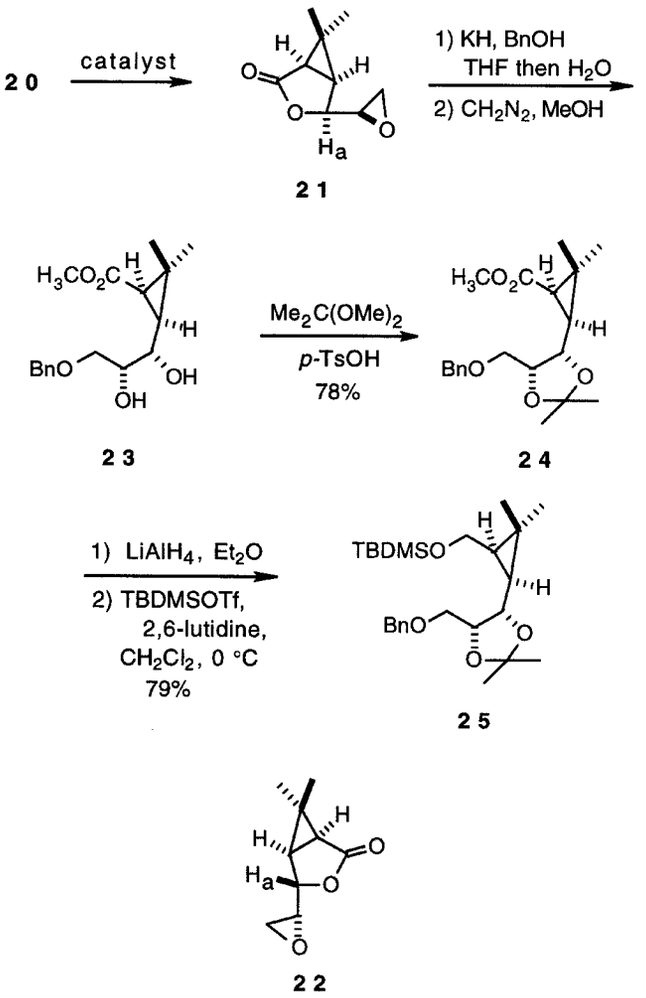
Cyclization of **20** in the presence of $Rh_2[(5S)MEPY]_4$ gave an inseparable mixture (5:1) of the desired *endo* adduct **21** together with the *exo* adduct **22** in 70% combined yield (Scheme VIII). When this reaction was catalyzed with $Cu(TBS)_2$, a mixture (1:7) of the diastereomeric cyclopropyl lactones **21** and **22** (74%) was produced. However, use of the enantiomeric rhodium catalyst $Rh_2[(5R)$-MEPY$]_4$ gave very little of either cyclopropanation product **21** or **22**, presumably owing to a chiral mismatch between the catalyst and substrate. The structures of the diastereomeric lactones **21** and **22** were readily assigned based upon their ^{1}H NMR spectra because there are differences in the characteristic chemical shifts and splitting patterns for the bridgehead protons labeled as H_a in each.[3a,c] Thus, for the *endo* product **21**, the signal for H_a appeared as a doublet of doublets (J = 4.6, 10.0 Hz) at 4.30 ppm, whereas in the *exo* adduct **22** the H_a proton is a simple doublet (J = 9.6 Hz) at 4.00 ppm.

To complete the synthesis of the fully functional cyclopropane subunit in **14**, the mixture of **21** and **22** was treated with excess potassium benzyloxide in THF to open the epoxide. Subsequent hydrolysis of the lactone moiety followed by esterification of the intermediate acid delivered the ester **23** in 16% overall yield. The opening of the epoxide ring and the hydrolysis of the lactone moiety were the problematic steps in this sequence, which has not yet been optimized. Protection of the diol as its isopropylidene acetal via the combined action of 2,2-dimethoxypropane and *p*-toluenesulfonic acid afforded **24** in 78% yield.[17] Subsequent reduction of the methyl ester with $LiAlH_4$ and protection of the resultant alcohol with TBDSMOTf in the presence of 2,6-lutidine provided **25** in 79% yield for the two steps. Compound **25** comprises the requisite right-hand portion of ingol B. Studies are currently underway in our laboratories towards optimizing this sequence and completing the total synthesis of ingol B (**14**).

CONCLUSION

It is now apparent that the diastereoselectivity of the intramolecular cyclopropanations of secondary allylic diazoacetates can be controlled to a significant degree through the choice of catalyst. For example, when an achiral catalyst such as $Cu(TBS)_2$ is employed, a reasonable degree of selectivity (typically 2.5-5:1) in the intramolecular cyclopropanation is observed. This diastereofacial selectivity can be reversed using a matched chiral catalyst such as $Rh_2[(5S)$-MEPY$]_4$ or $Rh_2[(5R)$-MEPY$]_4$. Indeed use of a chiral catalyst can lead to selectivities as high as 20:1. Not only has this methodology been applied to the syntheses of novel, biologically active peptide mimics, but it may also be used in natural product synthesis. Further applications of diastereoselective cyclopropanations are under active investigation, and the results will be reported in due course.

Scheme VIII



EXPERIMENTAL SECTION

General

All reagents obtained from commercial sources were used without further purification unless otherwise indicated. Tetrahydrofuran (THF) and diethyl Et_2O (Et_2O) were distilled from potassium and benzophenone. Dichloromethane (CH_2Cl_2), benzene, diisopropylamine, 2,6-lutidine, acetonitrile (CH_3CN), and triethylamine were distilled from calcium hydride, and dimethylsulfoxide (DMSO) was dried over 3 Å sieves. All air and/or moisture sensitive reactions were run under an argon atmosphere in oven dried glassware. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh ASTM).[18] Percent yields are given for compounds that were ≥95% pure as judged by NMR or HPLC. Melting points are uncorrected. Infrared (IR) spectra were recorded as solutions in $CHCl_3$ unless noted otherwise and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained at the indicated field as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts for ^1H and ^{13}C NMR spectra are reported in parts per million (ppm, δ) downfield relative to internal tetramethylsilane (TMS); for ^{13}C spectra TMS was referenced to the center line of the $CDCl_3$ triplet (δ 77.0). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; and br, broad.

(1*S*,5′*R*)-1-(2′,2′-Dimethyl-[1′,3′]dioxolan-4-yl)-3-phenyl-prop-2-yn-ol (5)

To a dry, argon flushed round-bottom flask containing iodobenzene (73 μL, 0.65 mmol), $Pd(Ph_3P)_4$ (37 mg, 0.032 mmol), and CuI (12 mg, 0.064 mmol) in dry pyrrolidine (distilled from BaO, 1 mL) was added the alkyne **4**[4] (100 mg, 0.64 mmol) in dry pyrrolidine (1 mL). The dark-brown solution was stirred for 2.5 h, whereupon solid NH_4Cl (25 mg), H_2O (1

mL) and Et_2O (5 mL) were added. The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organics were dried ($MgSO_4$), and concentrated, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to give 138 mg (94%) of **5** as an orange oil; ^{1}H NMR δ 7.46-7.26 (comp, 5H), 4.70 (t, *J* = 4.2 Hz, 1H), 4.34 (dt, *J* = 4.2, 6.4 Hz, 1H), 4.17-4.08 (m, 2H), 2.88 (d, *J* = 4.8 Hz, 1H), 1.50 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 131.7, 128.6, 128.2, 122.1, 110.1, 86.1, 86.0, 78.0, 65.3, 63.0, 62.9, 26.3, 25.2; IR ($CDCl_3$) ν 3440, 1644 cm^{-1}; mass spectrum (CI) *m/z* 233.1178 ($C_{14}H_{16}O_3$ + H requires 233.1176) 215 (base), 203, 191, 175, 157, 145, 129.

(1*R*,5′*R*)-1-*p*-Nitrobenzoic acid-1-(2′,2′-dimethyl-[1′,3′]dioxolan-4′-yl)-1-phenyl-prop-2-ynyl ester

To a solution of *p*-nitrobenzoic acid (351 mg, 2.1 mmol), triphenylphosphine (552 mg, 2.1 mmol) and the alkyne **5** (350 mg, 1.51 mmol) in dry THF/benzene (6 mL; 1:1) at 0 °C was slowly added DEAD (diethyl diazodicarboxylate, 330 μL, 2.1 mmol). The dark orange mixture was stirred overnight at rt, whereupon the solvent was removed under reduced pressure. The oily residue was diluted with Et_2O (20 mL) and placed in a refrigerator overnight. The precipitated triphenylphosphine oxide was removed by filtration, and the filtrate was concentrated. The residue was purified via flash chromatography eluting with EtOAc/hexanes (1:4). Subsequent recrystallization of the slightly colored material from Et_2O/hexanes yielded 405 mg (70%) of the *p*-nitrobenzoyl ester as white needles: m.p. 98.5-101 °C; ^{1}H NMR δ 8.30 (s, 4H), 7.47-7.43 (comp, 2H), 7.36-7.26 (comp, 3H), 5.93 (d, *J* = 7.7 Hz, 1H), 4.55 (ddd, *J* = 5.1, 6.4, 7.7 Hz, 1H), 4.27 (dd, *J* = 6.4, 9.1 Hz, 1H), 4.19 (dd, *J* = 5.1, 9.1 Hz, 1H), 1.49 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 163.6, 150.8, 135.1, 132.0, 131.1, 129.2, 128.4, 123.5, 121.5, 111.0, 87.5, 82.6, 77.4, 67.5, 66.4, 26.6, 25.4; IR ($CDCl_3$) ν 2990, 1732, 1530, 1266 cm^{-1}; mass spectrum (CI) *m/z* 382.1279 ($C_{21}H_{19}NO_6$ + H requires 382.1291) 354, 296, 215 (base), 197, 185, 157.

(1*R*,5′*R*)-1-(2′,2′-Dimethyl-[1′,3′]dioxolan-4-yl)-3-phenyl-prop-2-yn-ol (7)

To a solution of NaOH (51 mg, 1.26 mmol) in dry MeOH (3 mL) was added *p*-nitrobenzoyl ester from the preceding reaction (205 mg, 0.538 mmol) in dry THF (1 mL), and the reaction was stirred for 0.5 h. Solvent was removed under reduced pressure and Et_2O (20 mL) and water (5 mL) were added. The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organics were dried ($MgSO_4$) and concentrated, and the residue was purified via flash chromatography eluting with EtOAc/hexanes (1:2.5) to give 113 mg (90%) of **7** as a clear oil; ^{1}H NMR δ 7.45-7.26 (comp, 5H), 4.56 (dd, *J* = 4.2, 7.1 Hz, 1H), 4.29 (dt, *J* = 5.7, 6.6 Hz, 1H), 4.16 (dd, *J* = 6.6, 8.7 Hz, 1H), 3.99 (dd, *J* = 5.7, 8.7 Hz, 1H), 2.66 (d, *J* = 4.2 Hz, 1H), 1.49 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 131.8, 128.7, 128.3, 122.0, 110.5, 86.2, 86.0, 78.8, 66.2, 64.8, 26.8, 25.3; IR ($CDCl_3$) ν 3441, 1656, 1490, 1373, 1216, 1070 cm^{-1}; mass spectrum (CI) *m/z* 232.1099 ($C_{14}H_{15}O_3$ + H requires 232.1097) 215 (base), 185, 175, 157, 145, 129.

***cis*-(1*S*,5′*R*)-1-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-3-phenyl-prop-2-en-1-ol**

To a green suspension of $Ni(OAc)_2 \cdot H_2O$ (183 mg, 0.73 mmol) in absolute EtOH (4 mL) under argon was added $NaBH_4$ (28 mg, 0.73 mmol) in 0.1 N NaOH/EtOH (730 μL). After 45 min the flask was flushed with hydrogen, and ethylenediamine and **5** (509 mg, 2.19 mmol) absolute EtOH (0.5 mL) were added. A hydrogen filled balloon was attached and the mixture was stirred under H_2 (1 atm) for 2 h. Et_2O/pentane (100 mL, 1:1) was added, and the black suspension was filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the crude oily residue was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to give 475 mg (93%) of the (*Z*)-*erythro* allylic alcohol as a clear oil; ^{1}H NMR δ 7.35-7.21 (comp, 5H), 6.72 (d, *J* = 11.7 Hz, 1H), 5.61 (dd, *J* = 9.3, 11.7 Hz, 1H), 4.70 (dd, *J* = 4.8, 9.3 Hz, 1H), 4.18 (ddd, *J* = 4.8, 6.6, 6.8 Hz, 1H), 4.04 (dd, *J* = 6.6, 8.2 Hz, 1H), 3.95 (dd, *J* = 6.8, 8.2 Hz, 1H), 2.31 (br s, 1H), 1.43 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 136.1, 134.1, 128.9, 128.6, 128.3, 127.5, 109.4, 78.0, 67.5, 65.3, 26.2, 25.0; IR ($CDCl_3$) ν 3426, 1633, 1372, 1211, 1155, 1062 cm^{-1}; mass spectrum (CI) *m/z* 235.1328 ($C_{14}H_{18}O_3$ + H requires 235.1334) 217 (base), 177, 159, 129, 117.

***cis*-(1*R*,5′*R*)-1-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-3-phenyl-prop-2-en-1-ol**

Prepared in 86% yield as a clear oil from **7** according to the same procedure described for the (*Z*)-*erythro* allylic alcohol above. ^{1}H NMR δ 7.40-7.21 (comp, 5H), 6.68 (d, *J* = 11.8 Hz, 1H), 5.64 (dd, *J* = 9.7, 11.8 Hz, 1H), 4.46 (m, 1H), 4.12 (dt, *J* = 6.0, 6.4 Hz, 1H), 3.96 (dd, *J* = 6.4, 8.4 Hz, 1H), 3.68 (dd, *J* = 6.0, 8.4 Hz, 1H), 2.62 (d, *J* = 4.3 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR δ 136.1, 134.3, 128.7, 128.6, 128.3, 127.5, 109.7, 79.1, 68.5, 65.7, 26.6, 25.2; IR ($CDCl_3$) ν 3451, 2985, 1371, 1259, 1213, 1066 cm^{-1}; mass spectrum (CI) *m/z* 235.1334 ($C_{14}H_{18}O_3$ + H requires 235.1334), 217 (base), 177, 159, 129, 101.

***trans*-(1*S*,5′*R*)-1-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-3-**

phenyl-prop-2-en-1-ol

A solution of **5** (250 mg, 1.076 mmol) in dry Et_2O (1 mL) was slowly added to a solution of Red-Al (0.5 mL, 1.73 mmol) in dry Et_2O (1 mL) at 0 °C. This mixture was stirred for 10 min at 0 °C and at rt for 1 h, whereupon solid NH_4Cl (20 mg) and water (1 mL) were added very slowly (Caution! Very exothermic). The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 5 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude oily residue was purified by flash chromatography eluting with EtOAc/hexanes (1:1) to give 218 mg (87%) of the (*E*)-*erythro* allylic alcohol as a clear oil; ^{1}H NMR δ 7.39-7.21 (comp, 5H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.17 (dd, *J* = 5.6, 15.9 Hz, 1H), 4.47 (dd, *J* = 4.3, 5.6 Hz, 1H), 4.21 (dt, *J* = 4.3, 6.6 Hz, 1H), 4.10-3.92 (comp, 2H), 1.47 (s, 3H), 1.37 (s, 3H); ^{13}C NMR 136.3, 132.0, 131.9, 128.5, 127.8, 126.7, 126.6, 126.5, 109.5, 78.3, 71.7, 64.8, 26.4, 25.1; IR (neat) ν 3448, 2987, 1636, 1495, 1449, 1381, 1214, 1066 cm^{-1}; mass spectrum *m/z* 235.1334 ($C_{14}H_{18}O_3$ + H requires 235.1334) 217 (base), 177, 159, 133, 131, 129, 117, 101.

***trans*-(1*S*,5′*R*)-1-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-3-phenyl-prop-2-en-1-ol**

Prepared in 92% yield from **7** as a clear oil according to the same procedure described for the (*E*)-*erythro* allylic alcohol above; ^{1}H NMR δ 7.38-7.20 (comp, 5H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.12 (dd, *J* = 6.8, 15.9 Hz, 1H), 4.22 (m, 1H), 4.11 (dt, *J* = 6.0, 6.4 Hz, 1H), 3.99 (dd, *J* = 6.4, 8.4 Hz, 1H), 3.81 (dd, *J* = 5.8, 8.4 Hz, 1H), 2.86 (d, *J* = 3.6 Hz, 1H), 1.47 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 136.1, 132.9, 132.8, 128.4, 127.8, 127.0, 126.9, 109.8, 78.8, 73.9, 65.7, 26.7, 25.2; IR (neat) ν 3566, 2990, 2888, 1496, 1450, 1373, 2114, 1067 cm^{-1}; mass spectrum *m/z* 234.1256 ($C_{14}H_{17}O_3$ + H requires 234.1247) 217 (base), 177, 159, 133, 129, 101.

***cis*-(1*S*,5′*R*)-1-Diazoacetic acid 1-(2′,2′-dimethyl-[1′,3′]dioxolane-4′-yl)-3-phenyl-prop-2-enyl ester (6b)**

Prepared according to the method of Corey and Meyers[9] in 88% yield from the corresponding (*Z*)-*erythro* allylic alcohol as a yellow oil; ^{1}H NMR δ 7.41-7.23 (comp, 5H), 6.76 (d, *J* = 11.8 Hz, 1H), 5.93 (dd, *J* = 5.0, 9.5 Hz, 1H), 5.61 (dd, *J* = 9.5, 11.8 Hz, 1H), 4.78 (br s, 1H), 4.25 (dt, *J* = 5.0, 6.5 Hz, 1H), 4.02 (dd, *J* = 6.5, 8.4 Hz, 1H), 3.79 (dd, *J* = 6.5, 8.4 Hz, 1H), 1.34 (s, 6H); ^{13}C NMR δ 135.9, 134.8, 128.5, 128.4, 127.6, 125.5, 109.8, 76.6, 70.9, 65.7, 46.3, 26.0, 25.2; IR ($CDCl_3$) ν 2115, 1694, 1354, 1180 cm^{-1}; mass spectrum (CI) *m/z* 303.1341 ($C_{16}H_{18}N_2O_4$ + H requires 303.1345) 275, 245, 233, 217 (base), 199, 187, 159, 129, 117.

***cis*-(1*R*,5′*R*)-1-Diazoacetic acid 1-(2′,2′-dimethyl-[1′,3′]dioxolane-4′-yl)-3-phenyl-prop-2-enyl ester (8b)**

Prepared according to the same procedure as **6b** from the corresponding (*Z*)-*threo* allylic alcohol in 80% yield as a yellow oil; ^{1}H NMR δ 7.44-7.17 (comp, 5H), 6.71 (d, *J* = 11.8 Hz, 1H), 5.93 (dd, *J* = 5.5, 9.8 Hz, 1H), 5.62 (dd, *J* = 9.8, 11.8 Hz,1H), 4.77 (br s, 1H), 4.26 (dt, *J* = 5.5, 6.8 Hz, 1H), 3.98 (dd, *J* = 6.8, 8.9 Hz, 1H), 3.76 (dd, *J* = 5.5, 8.9 Hz, 1H), 1.39 (s, 3H), 1.34 (s, 3H); ^{13}C NMR δ 135.8, 134.5, 128.5, 128.4, 127.7, 125.4, 110.0, 71.2, 65.3, 26.2, 25.3; IR ($CDCl_3$) ν 2984, 2108, 1690, 1370, 1176, 1063 cm^{-1}; mass spectrum (CI) *m/z* 303.1346 ($C_{16}H_{18}N_2O_4$ + H requires 303.1345) 275, 247, 217 (base), 199, 177, 159, 143, 129, 117.

***trans*-(1*S*,5′*R*)-1-Diazoacetic acid 1-(2′,2′-dimethyl-[1′,3′]dioxolane-4′-yl)-3-phenyl-prop-2-enyl ester (6a)**

Prepared according to the same procedure as **6b** from the corresponding (*E*)-*erythro* allylic alcohol in 68% yield as a yellow oil; ^{1}H NMR δ 7.41-7.23 (comp, 5H), 6.69 (d, *J* = 15.8 Hz, 1H), 6.19 (dd, *J* = 7.1, 15.8 Hz, 1H), 5.58 (dd, *J* = 4.8, 7.1 Hz, 1H), 4.84 (br s, 1H), 4.31 (ddd, *J* = 4.8, 6.4, 6.7 Hz, 1H), 4.08 (dd, *J* = 6.7, 8.4 Hz, 1H), 3.86 (dd, *J* = 6.4, 8.4 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 135.9, 134.6, 128.5, 128.2, 126.7, 123.0, 110.0, 76.6, 74.5, 65.8, 46.6, 26.3, 25.2; IR ($CDCl_3$) ν 2986, 2112, 1693, 1372, 1237, 1178, 1068, 969 cm^{-1}; mass spectrum (CI) *m/z* 303.1345 ($C_{16}H_{18}N_2O_4$ + H requires 303.1351), 287, 275, 259, 245 217 (base), 159.

***trans*-(1*R*,5′*R*)-1-Diazoacetic acid 1-(2′,2′-dimethyl-[1′,3′]dioxolane-4′-yl)-3-phenyl-prop-2-enyl ester (8a)**

Prepared according to the same procedure as **6b** from the corresponding (*E*)-*threo* allylic alcohol in 73% yield as a yellow oil; ^{1}H NMR δ 7.41-7.24 (comp, 5H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.12 (dd, *J* = 7.8, 15.9 Hz, 1H), 5.55 (rotameric dd, *J* = 6.4, 7.8 Hz, 1H), 4.82 (br s, 1H), 4.30 (dt, *J* = 5.7, 6.4 Hz, 1H), 4.03 (dd, *J* = 6.6, 8.8 Hz, 1H), 3.83 (dd, *J* = 5.7, 8.8 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 135.7, 135.4, 128.6, 128.3, 126.7, 122.9, 110.1, 75.4, 65.7, 46.6, 26.4, 25.3; IR ($CDCl_3$) ν 2985, 2111, 1694, 1373, 1238, 1179, 1069 cm^{-1}; mass spectrum (CI) *m/z* 302.1267 ($C_{16}H_{17}N_2O_4$ + H requires 302.1253), 287, 275, 245, 217 (base).

General Procedure for the Cyclopropanation of 6a,b and 8a,b

To a refluxing solution of $Cu(TBS)_2$ (0.02 mol eq.) in toluene or Rh_2[(5*S*)-MEPY]$_4$ or Rh_2[(5*R*)-MEPY]$_4$ (0.01 mol equiv) in CH_2Cl_2 (0.02 M) was added a solution of the substrate (1 mol equiv) in CH_2Cl_2 (0.1 M) over 16-18 h. The reaction was cooled to rt, and solvent removed via rotary evapora-

tion under reduced pressure, and the crude product was purified by either flash chromatography or by filtration through a plug of silica, concentration of the filtrate, and recrystallization of the crude product.

(1*R*,4*S*,5*S*,6*S*,5′*R*)-4-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (9a)

Prepared from **6a** according to the general procedure for cyclopropanation; ^{1}H NMR σ 7.34-7.05 (comp, 5H), 4.35 (d, *J* = 7.7 Hz, 1H), 4.16 (dd, *J* = 6.2, 8.4 Hz, 1H), 4.07 (ddd, *J* = 4.0, 6.2, 7.7 Hz, 1H), 3.99 (dd, *J* = 4.0, 8.4 Hz, 1H), 2.71 (dd, *J* = 4.6, 5.2 Hz, 1H), 2.32 (d, *J* = 4.6 Hz, 2H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 174.2, 137.3, 129.1, 127.6, 126.2, 110.6, 81.2, 77.8, 66.8, 29.2, 28.6, 27.5, 25.2; IR (neat) ν 3524, 2992, 1769, 1604, 1500, 1456, 1383, 1258, 1067 cm^{-1}; mass spectrum (CI) *m/z* 275.1282 ($C_{16}H_{18}O_4$ + H requires 275.1283) 259, 245, 217, 199, 171, 129.

(1*R*,4*S*,5*S*,6*R*,5′*R*)-4-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (9b)

Prepared from **6b** according to the general procedure for cyclopropanation: m.p. 157-158 °C; ^{1}H NMR δ 7.36-7.24 (comp, 5H), 4.11-4.03 (comp, 2H), 3.98-3.96 (m, 1H), 3.84 (dd, *J* = 3.4, 4.8 Hz, 1H), 2.80 (t, *J* = 8.4 Hz, 1H), 2.71 (dd, *J* = 6.0, 8.4 Hz, 1H), 2.56 (ddd, *J* = 0.9, 6.0, 8.4 Hz, 1H), 1.45 (s, 3H), 1.34 (s, 3H); ^{13}C NMR δ 173.71, 132.6, 129.3, 129.0, 127.8, 110.1, 76.2, 66.5, 26.8, 26.3, 25.9, 25.0, 23.7; IR (neat) ν 3081, 2941, 1764, 1370, 1155, 1057, 981 cm^{-1}; mass spectrum (CI) *m/z* 275.1281 ($C_{16}H_{18}O_4$ + H requires 275.1283) 217, 199, 186, 173, 154.

(1*S*,4*S*,5*S*,6*S*,5′*R*)-4-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (10b)

Prepared from **6b** according to the general procedure for cyclopropanation: m.p. 133-134 °C; ^{1}H NMR δ 7.49-7.27 (comp, 5H), 4.48 (dd, *J* = 4.8, 9.5 Hz, 1H), 3.75 (dd, *J* = 5.7, 8.4 Hz, 1H), 3.62 (dd, *J* = 4.6, 8.8 Hz, 1H), 3.57 (ddd, *J* = 4.6, 5.7, 9.5 Hz, 1H), 2.85 (dd, *J* = 8.5, 8.9 Hz, 1H), 2.65 (ddd, *J* = 4.8, 6.0, 8.5 Hz, 1H), 2.61 (dd, *J* = 6.0, 8.9 Hz, 1H), 1.46 (s, 3H), 1.29 (s, 3H); ^{13}C NMR δ 173.9, 134.1, 129.0, 128.4, 127.4, 109.2, 80.1, 71.7, 68.2, 27.2, 26.8, 25.9, 24.8, 23.5; IR (neat) ν 2989, 2934, 1770, 1372, 1157, 1059, 996 cm^{-1}; mass spectrum (CI) *m/z* 277.1279 ($C_{16}H_{18}O_4$ + H requires 275.1283) 259, 217, 199 (base), 171, 155, 143, 129, 111.

***trans*-(5*R*,6*S*)-2,2-Dimethyl-6-(2′-Phenylethene)-1,3,7-trioxaspiro[4.4]nonane-8-one (11a)**

Prepared from **6a** according to the general procedure for cyclopropanation with Rh_2[(5*S*)-MEPY]$_4$; ^{1}H NMR δ 7.43-7.24 (comp, 5H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.32 (dd, *J* = 7.6, 15.9 Hz, 1H), 4.83 (d, *J* = 7.6 Hz, 1H), 4.05 (d, *J* = 9.1 Hz, 2H), 2.78 (d, *J* = 17.5 Hz, 2H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 173.5, 135.7, 125.5, 128.7, 128.5, 126.8, 121.5, 111.8, 86.0, 84.5, 70.5, 40.8, 26.4, 25.9; IR ($CDCl_3$) ν 2986, 1787, 1214, 1072, 973 cm^{-1}; mass spectrum (CI) *m/z* 275.1285 ($C_{16}H_{18}O_4$ + H requires 275.1283) 245, 217 (base), 199, 157.

***cis*-(5*R*,6*S*)-2,2-Dimethyl-6-(2′-Phenylethene)-1,3,7-trioxaspiro[4.4]nonane-8-one (11b)**

Prepared from **6b** according to the general procedure for cyclopropanation with Rh_2[(5*S*)-MEPY]$_4$; ^{1}H NMR δ 7.40-7.26 (comp, 5H), 6.0 (d, *J* = 11.5 Hz, 1H), 5.99 (dd, *J* = 9.5, 11.5 Hz, 1H), 5.0 (d, *J* = 9.5 Hz, 1H), 3.88 (d, *J* = 9.1 Hz, 2H), 2.76 (d, *J* = 17.6 Hz, 2H), 1.43 (s, 3H), 1.42 (s, 3H); ^{13}C NMR δ 173.7, 138.1, 135.5, 128.6, 128.5, 128.0, 122.7, 111.6, 84.3, 80.3, 70.3, 41.1, 26.4, 25.9; IR ($CDCl_3$) ν 2987, 2936, 1785, 1256, 1215, 1067, 984 cm^{-1}; mass spectrum (CI) *m/z* 275.1276 ($C_{16}H_{18}O_4$ + H requires 275.1283) 245, 217 (base), 199, 157.

(1*S*,4*R*,5*S*,6*S*,5′*R*)-4-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (12a)

Prepared from **8a** according to the general procedure for cyclopropanation; ^{1}H NMR δ 7.34-7.06 (comp, 1H), 4.51 (d, *J* = 2.1 Hz, 1H), 4.29 (dt, *J* = 2.3, 6.8 Hz, 1H), 4.13 (dd, *J* = 6.8, 8.4 Hz, 1H), 4.02 (dd, *J* = 7.1, 8.4 Hz, 1H), 2.48 (dd, *J* = 3.9, 5.9 Hz, 1H), 2.40 (dd, *J* = 3.1, 5.9 Hz, 1H), 2.29 (dd, *J* = 3.1, 3.7 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H); ^{13}C NMR δ 174.0, 136.9, 128.6, 127.0, 125.7, 110.2, 78.7, 76.6, 65.0, 28.2, 28.1, 27.4, 25.7, 25.3; IR (neat) ν 2987, 2936, 2891, 1770, 1604, 1499, 1457, 1372, 1217, 1065 cm^{-1}; mass spectrum (CI) *m/z* 275.1277 ($C_{16}H_{18}O_4$ + H requires 275.1283) 259, 245, 217, 199, 171, 143, 129.

(1*R*,4*R*,5*S*,6*S*,5′*R*)-4-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (13a)

Prepared from **8a** according to the general procedure for cyclopropanation; ^{1}H NMR δ 7.34-7.04 (comp, 5H), 4.63-4.60 (m, 1H), 4.30 (dt, *J* = 6.6, 6.7 Hz, 1H), 4.16 (dd, *J* = 6.7, 8.5 Hz, 1H), 3.86 (dd, *J* = 6.7, 8.5 Hz, 1H), 2.67 (dd, *J* = 3.2, 3.4 Hz, 1H), 2.40-2.39 (comp, 2H), 1.45 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 173.5, 136.8, 128.8, 127.4, 126.1, 110.7, 107.3, 79.5, 65.8 31.5, 27.0, 25.9, 22.6, 14.2; IR (neat) ν 2986, 1771, 1371, 1258, 1189, 1066, 984 cm^{-1}; mass spectrum (CI) *m/z* 275.1276 ($C_{16}H_{18}O_4$ + H requires 275.1283) 259, 245, 217, 199, 174, 144.

(1*S*,4*R*,5*S*,6*R*,5′*R*)-4-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (12b)

Prepared from **8b** according to the general procedure for

cyclopropanation: m.p. 184-186 °C; ^{1}H NMR δ 7.37-7.26 (comp, 5H), 4.26 (dt, *J* = 2.3, 6.8 Hz, 1H), 4.13-4.12 (m, 1H), 4.03 (dd, *J* = 6.8, 8.4 Hz, 1H), 3.87 (dd, *J* = 7.1, 8.4 Hz, 1H), 2.77 (dd, *J* = 8.2, 8.8 Hz, 1H), 2.63 (dd, *J* = 6.1, 8.8 Hz, 1H), 2.57-2.52 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 173.8, 132.7, 129.3, 128.9, 127.8, 110.2, 76.8, 75.0, 65.0, 25.7, 25.4, 24.0; IR (neat) ν 2986, 2882, 1751, 1370, 1218, 1170, 1068, 970 cm^{-1}; mass spectrum (CI) *m/z* 275.1289 ($C_{16}H_{18}O_4$ + H requires 275.1283) 259, 245, 217, 199, 187, 171, 155, 143, 129.

(1*R*,4*R*,5*S*,6*R*,5′*R*)-4-(2′,2′-Dimethyl-[1′,3′]dioxolan-4′-yl)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (13b)

Prepared from **8b** according to the general procedure for cyclopropanation: m.p. 172-174 °C; ^{1}H NMR δ 7.37-7.27 (comp, 5H), 4.64 (dd, *J* = 5.0, 8.8 Hz, 1H), 4.10 (dd, *J* = 7.0, 8.3 Hz, 1H), 3.82 (dd, *J* = 6.6, 8.4 Hz, 1H), 3.56 (ddd, *J* = 6.6, 7.0, 8.8 Hz, 1H), 2.77 (dd, *J* = 8.2, 9.0 Hz, 1H), 2.65 (dd, *J* = 6.4, 9.0 Hz, 1H), 2.44 (ddd, *J* = 5.0, 6.4, 8.2 Hz, 1H), 1.38 (s, 3H), 1.15 (s, 3H); ^{13}C NMR δ 173.7, 134.4, 128.9, 128.6, 128.2, 127.8, 110.4, 81.9, 74.0, 65.2, 26.9, 26.6, 26.1, 25.5, 25.0, 24.0; IR (neat) ν 3029, 2999, 2881, 1759, 1372, 1195, 1072, 1004 cm^{-1}; mass spectrum (CI) *m/z* 275.1274 ($C_{16}H_{18}O$ + H 275.1283) 259, 245, 217, 199, 171, 143, 129, 111.

(4*R*,5*S*)-[2,2-Dimethyl-5-(2′-methylpropenyl)-[1,3]-dioxolane-4-yl]-methanol (18)

A slurry of iodo isopropylidene triphenylphosphorane (5.6 g, 13 mmol) in THF (16 mL) at -78 °C was treated dropwise with a solution of 1.4 M *n*-BuLi (9 mL, 13 mmol) over 10 min. The orange colored solution was then placed in an ice bath for 15 min while the reaction color became blood red. The mixture then was cooled to -78 °C, and a solution of the lactol **17**[15] (830 mg, 5.2 mmol) in THF (3.0 mL) was added. The cooling bath was removed, and the mixture was stirred at ambient temperature for 2 h. H_2O (1 mL) was added, and the reaction was diluted with Et_2O (50 mL). The resulting slurry was filtered through a pad of celite, and the filtrate was washed with H_2O (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified via column chromatography eluting with EtOAc/hexanes (1:4) to give 800 mg (83%) of **7** as an oil; ^{1}H NMR δ 5.25 (ddq, *J* = 1.3, 1.3, 9.0 Hz, 1H), 4.94 (dd, *J* = 6.6, 9.0 Hz, 1H), 4.20 (ddd, *J* = 5.0, 5.0, 6.6 Hz, 1H), 3.57 (m, 2H), 1.83 (br s, 1H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.72 (d, *J* = 1.3 Hz, 3H), 1.50 (s, 3H), 1.4 (s, 3H); ^{13}C NMR δ 138.8, 119.3, 108.2, 78.1, 73.9, 62.3, 28.0, 25.9, 25.3, 18.3; IR ($CDCl_3$) ν 3442, 2985, 2934, 1600, 1451, 1379, 1216, 1165, 1043 cm^{-1}; mass spectrum (CI) *m/z* 187.1309 ($C_{10}H_{18}O_3$ + H requires 187.1334) 169, 157, 143, 129 (base), 111.

(4*R*,5*S*)-*p*-Toluenesulfonic acid [2,2-dimethyl-5-(2′-methylpropenyl)-[1,3]-dioxolane-4-yl]methyl ester

A solution of **18** (2.02 g, 10.8 mmol) and tosylchloride (3.50 g, 18.4 mmol) in pyridine (21 mL) was stirred overnight at rt. The solvent was removed via azeotropic distillation with toluene, and the crude solid residue was dissolved in a mixture of CH_2Cl_2/H_2O (50 mL:50 mL). The biphasic mixture was separated, and the aqueous phase was re-extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was purified via column chromatography eluting with EtOAc/hexanes (1:20 to 1:3 gradient) to give 3.33 g (91%) of the tosylate as a viscous oil; ^{1}H NMR δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 5.08 (ddq, *J* = 1.2, 1.2, 9.0 Hz, 1H), 4.90 (dd, *J* = 6.6, 9.0 Hz, 1H), 4.27 (ddd, *J* = 4.7, 6.6, 6.6 Hz, 1H), 4.03 (dd, *J* = 4.7, 10.2 Hz, 1H), 3.90 (dd, *J* = 6.6, 10.2 Hz, 1H), 2.45 (s, 3H), 1.72 (d, *J* = 1.2 Hz, 3H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 144.7, 139.4, 129.7, 127.9, 118.4, 108.7, 75.1, 73.9, 68.8, 27.7, 25.8, 25.2, 21.5, 18.4; IR ($CDCl_3$) ν 2986, 2935, 1598, 1454, 1366, 1178, 986, 816 cm^{-1}; mass spectrum (CI) *m/z* 301.1101 ($C_{14}H_{21}O_5$ + H requires 301.1110) 283, 265, 111 (base).

(2*R*,3*S*)-1-Tosyloxy-4-hexene-5-methyl-2,3-diol (19)

A solution of the tosylate (3.33 g, 9.78 mmol) from the preceding reaction in MeOH (45 mL) and 1 N HCl (15 mL, 15 mmol) was stirred overnight at rt. The reaction was neutralized by addition of sat. $NaHCO_3$ (30 mL), and the organics were removed by evaporation under reduced pressure. The resultant crude product was partitioned between brine (20 mL), sat. NH_4Cl (20 mL) and CH_2Cl_2 (40 mL). The layers were separated, and the aqueous phase was re-extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated, and the residue was purified via column chromatography eluting with EtOAc/hexanes (1:1) to give 2.41 g (82%) of **19** as an oil which solidified into a waxy solid upon standing; ^{1}H NMR δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.16 (ddq, *J* = 1.2, 1.2, 8.9 Hz, 1H), 4.41 (dd, *J* = 5.1, 8.9 Hz, 1H), 4.17-4.07 (m, 2H), 3.81 (ddd, *J* = 5.1, 5.1, 10.2 Hz, 1H), 2.70 (br s, 1H), 2.45 (s, 3H), 2.14 (br s, 1H), 1.73 (d, *J* = 1.2 Hz, 3H), 1.67 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR δ 145.0, 139.2, 132.7, 129.9, 127.9, 122.2, 72.2, 70.9, 68.9, 25.9, 21.6, 18.4; IR ($CDCl_3$) ν 3415, 2915, 1598, 1448, 1356, 1175, 1096, 970, 815 cm^{-1}; mass spectrum (CI) *m/z* 301.1101 ($C_{14}H_{20}O_5S$ + H requires 301.1110) 283, 265, 173, 111 (base).

(1*S*,2*R*)-3-Methyl-1-oxyranyl-but-2-en-1-ol

The tosylate **19** (2.41 g, 8.00 mmol) was dissolved in dry-degassed MeOH (40 mL) and cooled to 0 °C, whereupon K_2CO_3 (1.11 g, 8.0 mmol) was added in one portion. After

stirring for 2 h, brine (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$) and concentrated, and the residue was purified via column chromatography eluting with Et_2O/Pentane (1:3) to give 900 mg (88%) of the epoxide as an oil; ^{1}H NMR δ 5.13 (ddq, *J* = 1.3, 1.3, 8.6 Hz, 1H), 4.61 (dd, *J* = 2.8, 8.6 Hz, 1H), 3.05 (ddd, *J* = 2.8, 2.8,4.0 Hz, 1H), 2.81 (dd, *J* = 2.8, 5.1 Hz, 1H), 2.74 (dd, *J* = 4.0, 5.1 Hz, 1H), 1.86 (br s, 1H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.75 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR δ 138.5, 122.2, 65.8, 54.0, 43.3, 25.8, 18.4; IR ($CDCl_3$) δ 3408, 2980, 2917, 1677, 1445, 1376, 1249, 1013, 827 cm^{-1}; mass spectrum (CI) *m/z* 129.0911 ($C_7H_{12}O_2$ + H requires 129.0916) 111 (base), 99, 93, 83.

(1*S*,2*R*)-1-Diazoacetic acid 3-methyl-1-oxyranyl-but-2-enyl ester (20)

A solution of the alcohol (865 mg, 6.75 mmol) prepared in the previous reaction and the *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (2.82 g, 10.8 mmol) in CH_2Cl_2 (34 mL) was cooled to 0 °C and treated with *N*,*N*-DMA (1.37 mL, 10.8 mmol). After 15 min, Et_3N (4.7 mL, 34 mmol) was added, and the resultant orange slurry was stirred for 10 min at 0 °C, 15 min at rt. H_2O (40 mL) was added, and the organic solvents were removed by evaporation under reduced pressure. The aqueous residue was extracted with EtOAc/Hexane (1:4, 2 × 25 mL), and the combined organics were washed with 0.5 N HCl (40 mL), dried ($MgSO_4$), and concentrated. The residue was purified via flash chromatography eluting with EtOAc/hexanes (1:10) to give 1.14 g (86%) of **20** as a yellow oil; ^{1}H NMR δ 5.71 (dd, *J* = 3.4, 9.3 Hz, 1H), 5.13 (ddq, *J* = 1.3, 1.3, 9.4 Hz, 1H), 4.78 (br s, 1H), 3.12 (ddd, *J* = 2.6, 3.4, 4.0 Hz, 1H), 2.75 (dd, *J* = 4.0, 5.1 Hz, 1H), 2.61 (dd, *J* = 2.6, 5.1 Hz, 1H), 1.77 (dd, *J* = 1.3 Hz, 3H), 1.75 (dd, *J* = 1.3 Hz, 3H); ^{13}C NMR δ 140.7, 118.1, 70.5, 52.4, 46.3, 44.3, 25.8, 18.6; IR ($CDCl_3$) ν 3109, 2975, 2918, 2112, 1702, 1372, 1238, 1180 cm^{-1}; mass spectrum (CI) *m/z* 197.0924 ($C_9H_{12}N_2O_3$ + H requires 197.0926) 169, 154, 129, 111 (base).

(4*R*,5*S*,1′*S*,2′*R*)-2′-(4-Benzyloxymethyl-2,2-dimethyl-[1,3]-dioxolan-4-yl)-3′,3′-dimethyl-cyclopropanecarboxylic acid methyl ester (24)

To a solution of Rh_2[(5*S*)-MEPY]$_4$ (15 mg, 1.8 × 10^{-2} mmol) in CH_2Cl_2 (80 mL) was added **20** (180 mg, 0.91 mmol) in CH_2Cl_2 (10 mL) via syringe pump over 18 h. The reaction was cooled to rt, solvent was removed under reduced pressure, and the crude oily product was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to give 126 mg (70%) of an inseparable mixture (5:1) of the *endo* adduct **21** and the *exo* adduct **22** as an oil. This mixture (126 mg, 0.64 mmol) was diluted with THF (2 mL) and slowly added to a solution of 1.2 M potassium benzyloxide in THF (4.0 mL, 4.8 mmol) at 0 °C. The resulting orange-colored reaction was stirred overnight, and H_2O (0.5 mL) and EtOAc (20 mL) were then added. The layers were separated, and the organic phase was dried ($MgSO_4$), concentrated, and filtered through a plug of silica with EtOAc (30 mL) as the eluant. The filtrate was concentrated, and the crude material was dissolved in MeOH (5 mL) and treated with CH_2N_2 via a flame-polished pipette until the solution remained yellow. Excess CH_2N_2 was removed by bubbling argon through the solution using a polished pipette, and the solvent was removed by evaporation under reduced pressure. The crude product was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to give 31 mg (16%) of **23** as an oil; ^{1}H NMR δ 7.38-7.26 (comp, 5H), 4.54 (abq, *J* = 11.8 Hz, 2H), 4.23 (dd, *J* = 4.5, 10.0 Hz, 1H), 3.78 (ddd, *J* = 4.0, 4.3, 5.9 Hz, 1H), 3.68-3.59 (m, 2H), 3.61 (s, 3H), 1.57 (d, *J* = 8.7 Hz, 1H), 1.32 (s, 3H), 1.23 (dd, *J* = 8.7, 10.0 Hz, 1H), 1.21 (s, 3H).

The **23** (31 mg) thus obtained was immediately dissolved in 2,2 dimethoxypropane (1 mL) containing *p*-TsOH (1.9 mg, 0.01 mmol) under argon, and the solution was stirred at rt for 1 h. The acid was neutralized by addition of conc. NH_4OH (1 drop), and the solvent was removed by evaporation under reduced pressure. The crude material was purified via column chromatography eluting with EtOAc/ hexanes (1:3) to give 27 mg (78%) of **24**; ^{1}H NMR δ 7.34-7.26 (comp, 5H), 4.66 (d, *J* = 6.2, 10.2 Hz, 1H), 3.55 (abq, *J* = 12.4 Hz, 2H), 4.28 (dd, *J* = 6.2, 12.0 Hz, 1H), 3.53-3.52 (comp, 5H), 1.52 (d, *J* = 8.8 Hz, 1H), 1.48 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 1.20 (dd, *J* = 8.8, 10.0 Hz, 1H), 1.21 (s, 3H); ^{13}C NMR δ 171.9, 138.0, 128.3, 127.7, 127.6, 108.1, 76.1, 73.3, 72.9, 69.1, 51.4, 31.0, 29.5, 28.6, 25.5, 25.4, 14.1; IR ($CDCl_3$) ν 2986, 2951, 2866, 1726, 1439, 1378, 1201, 1152, 1094 cm^{-1}; mass spectrum (CI) *m/z* 349.2012 ($C_{20}H_{28}O_5$ + H requires 349.2015) 333 (base), 317.

(4*R*,5*S*,1′*S*,2′*R*)-[2′-(5-Benzyloxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-3′,3′-dimethyl-cyclopropyl]-methanol

A solution of **24** (129 mg, 0.37 mmol) in Et_2O (3 mL) was added dropwise to an ice-cooled suspension of LAH (35 mg, 0.93 mmol) in Et_2O (3 mL). The reaction was stirred for 2 h, whereupon H_2O (200 μL) and 10% aqueous NaOH (200 μL) were added sequentially. The resultant white suspension was diluted with Et_2O (5 mL), and the mixture was filtered through a pad of celite. The filtrate was concentrated, and the residue was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to afford 107 mg (90%) of the alcohol as a clear oil; ^{1}H NMR δ 7.36-7.26 (comp, 5H), 4.57 (abq, *J* = 12.1 Hz, 2H), 4.25 (ddd, *J* = 4.6, 6.0, 8.5 Hz, 1H), 4.03 (dd, *J* = 6.0, 10.7 Hz, 1H), 3.77 (dd, *J* = 5.6, 11.6 Hz, 1H), 3.66 (dd, *J* =

8.5, 9.3 Hz 1H), 3.51 (dd, J = 4.6, 9.4 Hz, 1H), 3.40 (dd, J = 10.0, 11.5 Hz, 1H), 2.70 (br s, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H), 0.97 (ddd, J = 5.6, 8.9, 10.0 Hz, 1H), 0.71 (dd, J = 8.9, 10.6 Hz, 1H); ^{13}C NMR δ 137.1, 128.4, 128.2, 128.0, 107.6, 75.6, 74.9, 73.7, 68.8, 59.4, 29.9, 28.9, 28.1, 25.4, 25.2, 19.0, 14.8; IR ($CDCl_3$) ν 3448, 2984, 2933, 2867, 1454, 1377, 1217, 1069, 1027 cm^{-1}; mass spectrum (CI) m/z 321.2073 ($C_{19}H_{28}O_4$ + H requires 321.2066) 303, 263 (base), 245, 215, 197.

(4*R*,5S,1′*S*,2′*R*)-4-Benzyloxymethyl-5-[2′-(tert-Butyl-dimethylsilanyloxymethyl)-3′,3′-dimethyl-cyclopropyl]-[1,3]dioxolane (25)

A solution of the alcohol (107 mg, 0.31 mmol) from the previous experiment in CH_2Cl_2 (3 mL) containing 2,6-lutidine (55 μL, 0.47 mmol) and TBDMSOTf (85 μL, 0.37 mmol) was stirred for 3 h at -78 °C. After adding H_2O (3 mL), the layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified via flash chromatography eluting with EtOAc/hexanes (1:10) to afford 118 mg (88%) of **25** as a clear oil; ^{1}H NMR δ 7.38-7.26 (comp, 5H), 4.58 (s, 2H), 4.25 (ddd, J = 3.5, 6.4, 7.6 Hz, 1H), 3.96 (dd, J = 6.4, 10.6 Hz, 1H), 3.71 (dd, J = 3.4, 9.9 Hz, 1H), 3.69 (dd, J = 7.5, 11.0 Hz, 1H), 3.58 (dd, J = 7.6, 10.0 Hz, 1H), 3.54 (dd, J = 8.0, 11.1 Hz, 1H), 1.48 (s, 3H), 1.34 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 0.89-0.87 (m, 1H), 0.88 (s, 9H), 0.71 (dd, J = 9.1, 10.7 Hz, 1H), 0.03 (s, 6H); ^{13}C NMR δ 138.4, 128.3, 127.6, 127.4, 107.9, 75.0, 73.4, 70.0, 60.0, 29.4, 29.0, 28.2, 25.9, 25.6, 25.3, 18.7, 18.2, 14.8, -5.3; IR ($CDCl_3$) ν 2998, 2930, 2858, 1472, 1378, 1252, 1219, 1079, 836 cm^{-1}; mass spectrum (CI) m/z 433.2768 ($C_{25}H_{40}O_4Si$ + H requires 433.2774) 377 (base), 359, 303, 245, 215.

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Key Words

Cyclopropanation; Enantioselective; Asymmetric catalysis; Diastereoselective.

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