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Chiral and flexible 2,4-pentanediol-tethered cyclopropanation of olefins with a carbenoid derived from a diazo ester to construct three stereogenic centers

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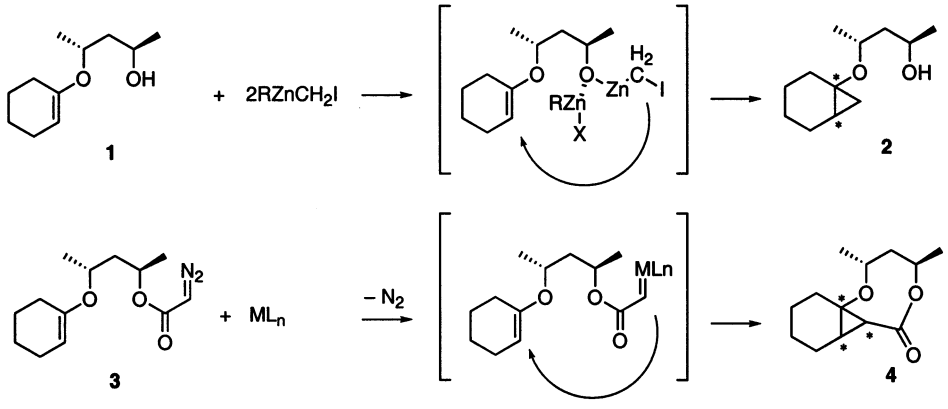
Abstract—2,4-Pentanediol-tethered cyclopropanation of an olefin with an internal carbenoid generated from a diazo ester proceeded smoothly to give a chiral adduct having three stereogenic centers under full stereocontrol. The high stereoselectivity was not affected by the structure of the olefinic portion, studied so far with six substrates. Conversion of the product cyclopropane to other optically active compounds is also reported. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Optically active 2,4-pentanediol is a member of the chiral pool commercialized by catalytic asymmetric syntheses,[1] and has been mainly utilized as a chiral auxiliary. Nucleophilic reactions of 2,4-pentanediol acetals of aldehydes (or ketones) were stereocontrolled by the stereogenic centers on the cyclic acetals to give adducts of 80% diastereomeric excess (de) in most cases.[2] An alternative reaction design using 2,4-pentanediol is the chiral tether reaction. 2,4-Pentanediol connects reactant and reagent moieties as a chiral and flexible tether; intramolecular reaction between the two moieties gives a product of over 99% de for many reactant/reagent combinations.[3,4] Cycloaddition to a prochiral olefin is a particular example. 2,4-Pentanediol enol ethers represented by **1** react with a zinc carbenoid first at the hydroxy group of the 2,4-pentanediol moiety, and then, the tethered carbenoid adds to the internal olefin to perform a stereoselective cyclopropanation (Scheme 1). Under optimized conditions, **2** in 97% de is obtained.[5]



Scheme 1. Quasi-intramolecular cyclopropanation of **1** with zinc carbenoid, and intramolecular cyclopropanation of **3** with metal catalyst.

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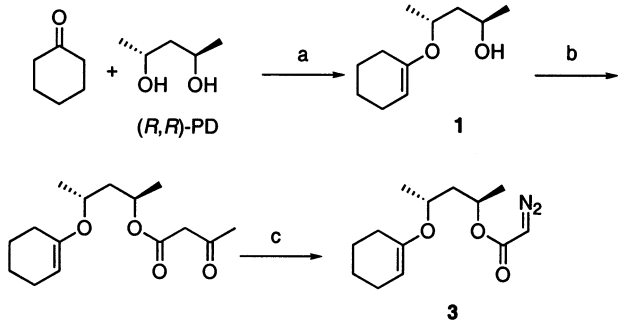
A drawback of this asymmetric cyclopropanation is that the contribution of non-hydroxy-directed intermolecular reactions is largely dependent on the reaction conditions, and cannot be sufficiently suppressed.

A counterplan to address the undesired intermolecular reactions in the 2,4-pentanediol tethered reaction is incorporation of a precursor of the reagent moiety to the tether through a covalent bond. The activated precursor moiety becomes the internal reactant under the stereocontrol of the 2,4-pentanediol tether. In this report, we would like to present the metal-catalyzed reaction of **3** carrying a diazo ester as a precursor of the carbenoid. The addition creates three new stereogenic centers; the product **4** has two functional groups, an electron-donating ether and withdrawing ester, which make the product valuable as a chiral synthon.[6] The scope and limitations in synthetic applications of the present asymmetric synthesis are also presented.[7]

2. Results and discussion

2.1. Catalysts and reaction conditions

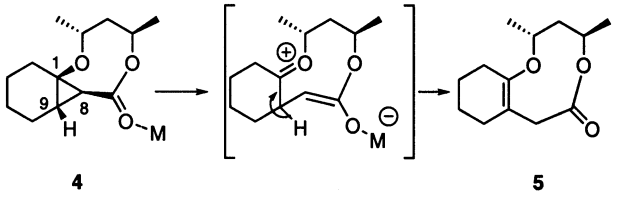
The substrate **3** was prepared from enantiomerically pure (*R*,*R*)-2,4-pentanediol in four steps through **1**. For the introduction of the acetoacetate ester to **1** (step b in Scheme 2), reaction with ketene in the presence of triethylamine resulted in a high yield of 97%, but an alternative method with methyl acetoacetate and *N*,*N*-4-dimethylaminopyridine catalyst under refluxing in benzene, can also be employed (98% yield) when diketene of good quality is not available. Introduction of a diazo group to give **3** could be achieved by a conventional procedure.



Scheme 2. *Reagents and conditions*: (a) *p*-TsOH/benzene reflux with Dean–Stark (98%), then triisobutylaluminum/CH_2Cl_2/−78°C (100%); (b) diketene/triethylamine/rt (97%); (c) TsN_3/triethylamine/rt, and then, aq. NaOH/rt/11 h (76%).

Typical catalysts for generation of metal carbenoids from a diazo ester were examined for the intramolecular cycloaddition of **3**.[8] Under gradual increase of, or at a fixed, temperature, the reaction was performed until complete consumption of **3** (Table 1, runs 1–3 and 4–6). The isolated yield of **4** much depended on the catalyst employed; $CuSO_4$ was found to be the best catalyst in terms of the product yield (92%, run 1). Use of $Rh_2(OAc)_4$ was also advantageous as its high catalytic activity allowed the reaction to be performed at room temperature though the isolated yield of **4** was moderate (77%, run 5). The major reason for the reduced yield is the instability of **3** under the reaction conditions resulting in hydrolysis of the enol ether part. When the catalyst was $Cu(OTf)_2$, the product **4** was also unstable and gave **5** during the reaction. The conversion of **4** to **5** in the presence of $Cu(OTf)_2$ was confirmed by the reaction with isolated **4** (quantitative yield, Scheme 3).

Through the reactions of runs 1–5 in Table 1, only one isomer of **4** was detected by ^1H NMR analysis. The stereochemistry of **4** was determined to be (1*R*,8*S*,9*S*) by NOE experiments (see Scheme 3 for the structure). The high stereochemical purity of **4** was confirmed as follows. When **1** was protected at the hydroxy group as a *t*-butyldimethylsilyl (TBS) ether and then heated with ethyl diazoacetate in the presence of $CuSO_4$, all four stereoisomers of **6** (**6a**–**d**) were obtained (Scheme 4). Their relative stereochemistries were determined by ^1H NMR spectroscopic analysis and interconversion by



Scheme 3. Isomerization of **4** to **5** catalyzed by $Cu(OTf)_2$.

Table 1. Metal-catalyzed reaction of **3** to give **4**

Run	Catalyst[a]	Solvent	Temp.	Isolated yield (%)	de (%)
1	$CuSO_4$	Benzene	Rt to 80	91.5	>99
2	$Cu(acac)_2$	Benzene	Rt to 80	78.1	>99
3	$Cu(OTf)_2$	Benzene	Rt to 80	0 (19.4)[b]	–
4	$Cu(OTf)_2$	Ether	Reflux	12.9 (16.6)[b]	>99
5	$Rh_2(OAc)_4$	CH_2Cl_2	Rt	77.1	>99
6	$Pd(OAc)_2$	Ether	Rt	0	–
7	$CuSO_4$	Toluene	110	46.5	92.2
8	$CuSO_4$	Xylene	138	–	88.2

[a] 2–3 mol% of catalyst was employed.
[b] Isolated yield of **5** is shown in parenthesis.

treatment with lithium diisopropylamide. The crude mixtures of **4** obtained from **3** were also converted to **6** by the treatment with sodium ethoxide in ethanol (**7**, 94% yield) followed by conversion to its TBS ether **6a** (66%). By a GLC analysis under the conditions separating all peaks of the four isomers of **6**, the samples derived from **4** of runs 1–5 showed a single peak. Thus, the stereoselectivity of the reaction of **3** at room temperature or at even higher (ca. 50°C estimated by the evolution of nitrogen) was determined to be sufficiently high so as to give **4** in over 99% de. However, when the $CuSO_4$-catalyzed reaction of **3** was performed at 110 or 138°C, the product **4** obtained was not stereochemically pure, and the GLC analysis after the conversion showed two peaks of **6a** and **6b**. The amounts of the minor isomer **6b** are 3.9 and 5.9%, respectively. The calculated de values of **4** are shown in Table 1, runs 7 and 8.

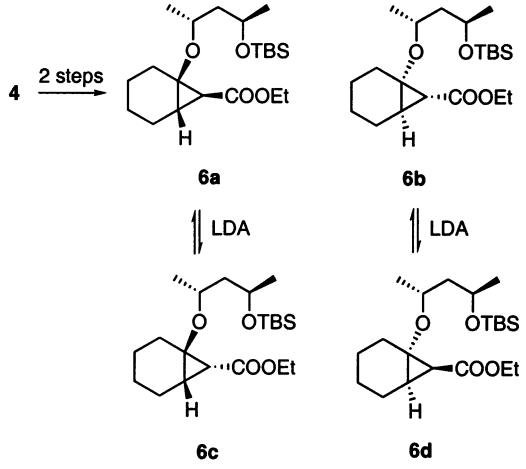
2.2. Ring opening of chiral cyclopropane 4

Reactions of **4** in stereochemically pure form (>99% de) were briefly studied to examine the possibility of its use as a chiral synthon. Ethanolysis of **4** to give **7** (precursor of **6a**) was not accompanied by epimerization. Acid treatment of **7** to cleave the cyclopropane ring gave **8** under anhydrous conditions and **9** in the presence of water (Scheme 5). Table 2 shows the isolated yields and de values obtained under different reaction conditions. During the isomerization to **8**, the stereochemical purity of **7** was partly lost in all cases, but to a degree much smaller than in the acid-catalyzed ring cleavage of **2** to a 2,4-pentanediol acetal.[5a] The epimerization must originate from the intermediacy of enol ether formation. The highest de of **8** so far studied was 79.1% (run 4). Substantial epimerization during the production of **9** was observed, but its levorotatory optical rotation clearly indicates a 2*S* configuration.[9] The structure of **7** is thus one of two stereoisomers corresponding to *cis*-**6a** or *trans*-**6c**. Since NOE was not observed between the protons on the cyclopropane ring, the *trans*-structure was discarded, and thus the stereochemistry of **4** was assigned as (1*R*,8*S*,9*S*).

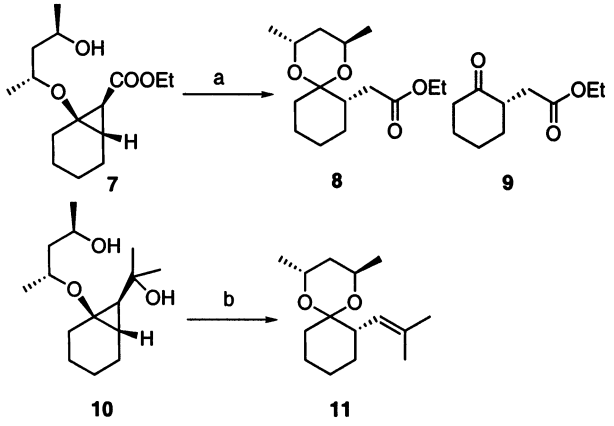
The results shown in Table 2, runs 1–4, indicate that the epimerization tends to be larger with stronger acid. Therefore, disuse of acid may facilitate the stereoretained ring opening. Treatment of **4** with 2 equiv. of methyllithium gave adduct **10** in 73% yield. When **10** was heated in HMPA at 150°C, dehydrative ring opening resulted in a 97.6% de of **11** in 84% yield. Thus, epimerization during the ring opening was minimized.

2.3. Effects of the tether on selectivity

In some other 2,4-pentanediol-tethered reaction systems, both methyl groups on the tether are not necessary to achieve a stereoselective reaction.[4,10] To investigate the stereocontrol of singly methylated tethers in the present system, three substrates **12**–**14** were synthesized in racemic form through a process related to that of **3**. The step-wise yields are given in Table 3.



Scheme 4. **6a** derived from **4** and its diastereomers.



Scheme 5. *Reagents and conditions*: (a) acid treatment; (b) HMPA/150°C (84%).

Table 2. Acid-catalyzed ring opening of **7** in benzene

Run	Acid	Temp.	Time (h)	Yield	de of **8**
1	AcOH	80	4.5	91	59.5
2	TsOH·pyridine	Rt	18	74	65.0
3	TsOH·collidine	80	7.5	98	73.3
4	AcOH·pyridine	80	44	73	79.1
5	$TsOH·H_2O$	Rt to 50	5.5	(52)[a]	(−0.6)[b]

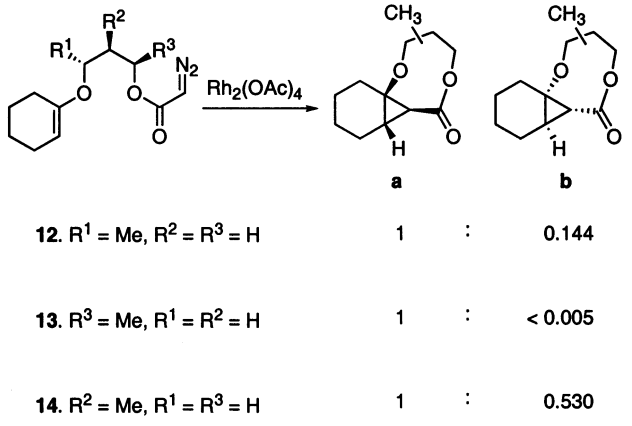
[a] Isolated yield of **9**.
[b] Optical rotation of **9**. Reported value for (2*S*)-isomer is −5.8 (methanol).[9]

Table 3. Yields of each step in the syntheses of diazo esters **12–19** via formation of acetals (**A**), isomerization to enol ethers (**B**), formation of acetoacetate esters (**C**), and conversion to the diazo esters, and yields and %de of the cyclopropane (**D**) obtained by the intramolecular addition of **12–19**

Substrate	A	B	C	Diazo ester	D	%de of D
12	100	98	76	70	48	75
13	100	50[a]	21[b]	84	51	>99
14	100	98	69	65	40	31
15	97	94	73	66	0–22 (55)[c]	>98
16	96	98	77	72	64	>98
17	88	98	90	66	55	>98
18	99[d]	78	19	46	22	>98
19	94	99	85	27 (71)[e]	39	>98

[a] Two step yields as a regioisomeric mixture (1:1) with pyridinium perbromide then Li/naphthalene/THF.
[b] Regioisomer (**12C**) was also obtained in 14% yield.
[c] TMEDA was added to the reaction mixture.
[d] 2-Methoxypropene (2 equiv.) was used instead of acetone.
[e] Eluent for the column chromatography included a trace amount of triethylamine.

Treatment of the substrates with $Rh_2(OAc)_4$ at room temperature gave intramolecular adducts (D in Table 3). All reactions resulted in lower isolated yields of the adducts than those with **3**. The stereochemistries of the adducts were assigned based on NOE experiments. The diastereomer ratios were determined in the same way as for **4**; ethanolysis, protection with a TBS group, and then GLC analysis. The results are summarized in Scheme 6. Stereocontrol of a singly methylated tether is moderate in **12**, but high in **13**, though the tether of **14** shows a poor control. The results of this series of experiments led to the conclusion that both of the methyl groups of **3** are not necessary for efficient stereoselectivity, but are indispensable to achieve effective intramolecular cycloaddition. It is also suggested that the 2,4-pentanediol tether having two methyl groups, which can work cooperatively in stereocontrol, must have quite high stereocontrol.



Scheme 6. Diastereocontrol with singly methylated tethers.

2.4. Application to different enol ethers

The strictly stereocontrolled 2,4-pentanediol-tethered cycloaddition of **3** was extended to substrates having different olefinic moieties. Substrates **15–19** shown in Figure 1 were prepared by the procedure used for **3** with some modifications. The step-wise yields are given in Table 3. Low yields in the syntheses of **18** and **19** are attributable to the instability of β-unsubstituted enol ether moieties. Decomposition during silica gel chromatography can be relieved by using an eluent containing a trace amount of triethylamine. An example is shown for the synthesis of **19**, where a 27% isolated yield by the standard method was improved to 71%. The intramolecular cycloaddition of **15–19** was carried out with $CuSO_4$ catalyst under the conditions of run 1 in Table 1. In all cases, the expected reaction was not as predominant as with **3**, and afforded lower isolated yields due to instability of the substrates especially in the case of **15**. One countermeasure is the presence of an appropriate base to control the decomposition of the enol ether moiety. In fact, addition of tetramethylethylenediamine (0.1 equiv.) to the reaction of **15** improved the yield to 55%. Although reactivities in the

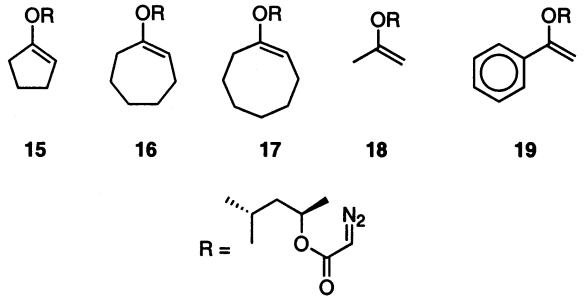


Figure 1. Structure for 2,4-pentanediol-tethered substrates.

intramolecular reaction are different among the substrates, the de values of the cycloadducts are over 98% for all the substrates. Thus, the stereocontrol of the 2,4-pentanediol tether was proven to be uniformly high, irrespective of the substrate structure.

3. Conclusion

By the present study, stereocontrol by the 2,4-pentanediol tether was again shown to be very high, and the versatility of the chiral tethered reaction for asymmetric

synthesis extended. With regard to the asymmetric cycloaddition of a diazo ester to a prochiral olefin, reactions using chiral catalysts have already been well documented, and many of them shown very high enantioface differentiation. However, their contorol in *cis*/*trans* structures is still not sufficient.[11] The present 2,4-pentanediol-tethered reaction is superior since it produces a single product. In addition, the high stereocontrol is not affected by the catalyst used; thus, the best choice of the catalyst for each substrate is possible. The origin of the stereocontrol of the 2,4-pentanediol-tethered reactions has been attributed to the differential activation entropy.[4] This study will give additional information for further analysis of this unusual stereocontrol mechanism.

4. Experimental

4.1. General

All temperatures are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL EXcalibur-400 spectrometer in $CDCl_3$ as a solvent and as internal standard (7.24 and 77.1 ppm). NOE experiments were conducted on a JEOL ECA-600 (^{1}H NMR, 600 MHz). IR spectra were obtained on a JASCO FT/IR-410 spectrometer. Mass spectra were obtained on a JEOL JMS-AX-505HA. Optical rotations were measured on a Perkin–Elmer 243B polarimeter. All dry solvents were distilled from calcium hydride. All reactions were carried out under a dry nitrogen atmosphere. Analytical GLC was conducted with a Shimadzu gas chromatograph GC-17A using a capillary column.

4.2. Preparation of 3

By the reported method,[5a] **1** was prepared from cyclohexanone and (*R*,*R*)-2,4-pentanediol in two steps. Ketene dimer (3.67 g, 1.15 equiv.) was added to a stirred solution of **1** (7.00 g, 0.038 mol) and triethylamine (2.1 ml, 0.4 equiv.) in dichloromethane (150 ml) at room temperature. The reaction mixture was stirred for 9 h, poured into water and extracted with dichloromethane (×3). The combined extracts were washed with water (×2) and brine (×2), dried over $MgSO_4$, and concentrated under vacuum to give a yellow oil. The oil was purified by silica gel chromatography (elution with 15% ethyl acetate in hexane) to give an acetoacetate ester as a colorless oil (9.92 g, 97.2% yield). $[\alpha]_D^{20}=-46.1$ (*c* 1.0, CH_2Cl_2); IR (neat) 1745, 1720, 1680 cm^{-1}; ^{1}H NMR δ 5.10 (m, 1H), 4.59 (t, $J=3.4$ Hz, 1H), 4.11 (m, 1H), 3.39 (s, 2H), 2.25 (s, 3H), 2.17–1.90 (m, 3H), 1.76–1.73 (m, 2H), 1.64 (quint, $J=6.1$ Hz, 2H), 1.56–1.42 (m, 2H), 1.26 (d, $J=6.1$ Hz, 3H), 1.25 (m, 1H), 1.18 (d, $J=5.9$ Hz, 3H); HRMS *m*/*z* (M+) calcd for $C_{13}H_{20}O_3$, 268.1675, obsvd 268.1595.

To a stirred solution of the acetoacetate ester (3.00 g, 0.0112 mol) and *p*-toluenesulfonyl azide (2.21 g, 1.0 equiv.) in dry acetonitrile (20 ml), triethylamine (5.45 ml, 3.49 equiv.) was added dropwise at 0°C over 5 min. After stirring for 2 h, the reaction mixture was allowed to warm up to room temperature, stirred for further 4 h, and then 1 M NaOH aq. (200 ml) was added to the stirred solution. The mixture was stirred for a further 11 h, and extracted with dichloromethane (100 ml×4). The combined extracts were washed with 1 M NaOH aq. (200 ml×2), dried (Na_2SO_4), and concentrated under vacuum to give a yellow oil (2.39 g, 83.6% crude yield). The oil was purified with a basic alumina column (elution with 3% ethyl acetate in hexane) to give **3** as a yellow oil (2.15 g, 76.0% yield). $[\alpha]_D^{20}=-73.4$ (*c* 1.0, CH_2Cl_2); IR (neat) 2110 and 1700 cm^{-1}; ^{1}H NMR δ 5.09 (m, 1H), 4.69 (s, 1H), 4.60 (t, $J=3.5$ Hz, 1H), 4.12 (m, 1H), 2.07–1.91 (m, 4H), 1.77–1.72 (m, 2H), 1.71–1.61 (m, 2H), 1.55–1.48 (m, 2H), 1.26 (d, $J=6.4$ Hz, 3H), 1.19 (d, $J=5.9$ Hz, 3H); MS *m*/*z* (M+−N_2) calcd for $C_{13}H_{20}O_3$, 224.1412, obsvd 224.1428.

4.3. Preparation of 4 (run 1 in Table 1)

A mixture of **3** (100 mg, 0.396 mmol) and dry $CuSO_4$ (1.28 mg, 0.02 equiv.) in dry benzene (2 ml) was gradually warmed up to reflux for 2 h. The mixture was allowed to cool to room temperature. Concentration of the mixture under vacuum gave a pale yellow oil. The oil was purified by silica gel chromatography (elution with 15% ethyl acetate in hexane) to give **4** as a colorless solid (81.3 mg, 91.5% yield). Mp 47.0–8.0; $[\alpha]_D^{20}=+35.3$ (*c* 1.0, MeOH); IR (KBr) 1730 cm^{-1}; ^{1}H NMR δ 4.81 (dqd, $J=17.1$, 6.2, 2.7 Hz, 1H, H-5), 3.33 (m, 1H, H-3), 2.09–1.98 (m, 2H), 1.90 (ddd, $J=15.1$, 9.6, 6.2 Hz, 1H), 1.75–1.69 (m, 2H), 1.63–1.57 (m, 2H), 1.52 (m, 1H), 1.37 (d, $J=7.6$ Hz, 1H, H-8), 1.34–1.23 (m, 2H), 1.32 (d, $J=6.2$ Hz, 3H), 1.10 (m, 1H), 1.09 (d, $J=6.1$ Hz, 3H); NOE enhancement between H-5 and H-8: 3.9%; ^{13}C NMR δ 173.8, 71.8, 65.6, 64.5, 48.0, 31.9, 30.4, 23.1, 22.0, 21.4, 21.24, 21.17, 21.16; MS *m*/*z* (M+) calcd for $C_{13}H_{20}O_3$, 224.1413, obsvd 224.1447.

When $Cu(OTf)_2$ was employed as a catalyst, **5** was obtained after column chromatography (runs 2 and 3). $[\alpha]_D^{20}=-107.5$ (*c* 1.16, CH_2Cl_2); IR (neat) 1740 cm^{-1}; ^{1}H NMR δ 5.11 (m, 1H), 3.92 (m, 1H), 2.81 (m, 1H), 2.63 (d, $J=16.5$ Hz, 1H), 2.22 (m, 2H), 2.04–1.87 (m, 3H), 1.70 (m, 1H), 1.63 (m, 2H), 1.47 (m, 1H), 1.39 (m, 1H), 1.24 (d, $J=6.9$ Hz, 6H); ^{13}C NMR δ 73.5, 147.9, 113.9, 71.4, 66.8, 39.4, 38.2, 29.4, 26.3, 23.2, 23.1, 22.4, 20.0; MS *m*/*z* (M+) calcd for $C_{13}H_{20}O_3$, 224.1413, obsvd 224.1403.

4.4. Preparation of 6a from 4

A solution of sodium ethoxide prepared from metallic sodium (2.0 g, 39 equiv.) and ethanol (10 ml) was added dropwise to a stirred solution of **4** (500 mg, 2.23 mmol) in ethanol (25 ml) over 5 min. The mixture was stirred for 1.3 h at room temperature, poured into a saturated aqueous solution of ammonium chloride, and extracted with diethyl ether (×3). The combined extracts were washed with water, dried (K_2CO_3), and concentrated under vacuum to give **7** as a colorless oil (568 mg, 94.3% yield). $[\alpha]_D^{20}=-31.3$ (*c* 0.416, MeOH); IR (neat) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13 (q, $J=7.1$ Hz, 2H), 3.98 (m, 1H), 3.89–3.82 (m, 2H), 2.25 (m, 1H), 2.16 (m,

1H), 2.13–1.95 (m, 2H), 1.66–1.59 (m, 3H), 1.55–1.29 (m, 5H), 1.26 (t, $J=7.1$ Hz, 3H), 1.19 (d, $J=6.1$ Hz, 3H), 1.11 (d, $J=6.1$ Hz, 3H); MS m/z (M+) calcd for $C_{15}H_{26}O_4$, 270.1831, obsvd 270.1797.

A mixture of *t*-butyldimethylsilyl chloride (25 mg, 4.2 equiv.), imidazole (23.3 mg, 8.5 equiv.), and *N*,*N*-dimethyl-4-aminopyridine (0.02 equiv.) in DMF (1 ml) was added to a stirred solution of **7** (11 mg, 0.04 mmol) in DMF (1 ml). The mixture was stirred for 15.5 h at room temperature, poured into a saturated aqueous solution of sodium bicarbonate, and extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under vacuum to give an oil. The oil was purified by silica gel chromatography (elution with diethyl ether) to give **6a** as a colorless oil (10.2 mg, 65.8% yield). $[\alpha]_D^{20}=+10.9$ (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 4.17–3.93 (m, 2H), 3.85 (m, 1H), 2.17–1.98 (m, 4H), 1.65–1.39 (m, 7H), 1.26 (t, $J=7.1$ Hz, 3H), 1.18 (m, 1H), 1.11 (d, $J=6.1$ Hz, 3H), 1.05 (d, $J=6.4$ Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); MS m/z (M+) calcd for $C_{21}H_{40}O_4Si$, 384.2696, obsvd 384.2645.

4.5. Preparation of an isomeric mixture of 6

A solution of *t*-butyldimethylsilyl chloride (2.78 g, 1.99 equiv.), imidazole (2.51 g, 4.00 equiv.), and *N*,*N*-dimethyl-4-aminopyridine (0.02 equiv.) in dimethylformamide (20 ml) was added dropwise to a stirred solution of **1** (1.70 g, 9.23 mmol) in dimethylformamide (20 ml) in 10 min. The mixture was stirred for 3.5 h at room temperature, poured into a saturated aqueous solution of sodium bicarbonate, and extracted with diethyl ether. The combined extracts were washed with brine, dried (K_2CO_3), and concentrated under vacuum to give an oil. The oil was purified by silica gel chromatography (elution with 3% ethyl acetate in hexane) to give a colorless oil (1.79 g, 64.8% yield). To a stirred mixture of the oil (512 mg, 1.72 mmol) and anhydrous $CuSO_4$ (1.28 mg, 0.02 equiv.) in benzene (3 ml) was added a solution of ethyl diazoacetate (43.5 mg, 2.2 equiv.) in benzene (5 ml). The mixture warmed up until reflux for 2 h, and concentrated under vacuum to give a yellow oil. The oil was purified by silica gel chromatography (elution with 20% ethyl acetate in hexane) to give **6** as a pale yellow oil (830 mg, 125.8% yield). GLC analysis (OV-1, id 0.25 mm×25 m, 155°C, 30 cm/s) showed four separated peaks at 80.1 (*trans*-**6d**, 26.4%), 82.1 (*cis*-**6a**, 20.7%), 84.8 (*trans*-**6c**, 19.3%), and 88.3 min (*cis*-**6b**, 33.6%). The mixture can be separated into *cis* (**6a** and **6b**) and *trans* (**6c** and **6d**) isomers by repeated column chromatography. Isomerization of **6a** or a mixture of **6a** and **6b** was performed by treatment with a stoichiometric amount of lithium diisopropylamide in THF at −78°C followed by quenching with water at the same temperature.

4.6. Preparation of 8 and 9 (Table 2, runs 4 and 5)

Pyridinium acetate was added to a solution of **7** (6.4 mg, 0.024 mmol) in benzene (2 ml). The mixture was stirred for 44 h under reflux, poured into water, and extracted with diethyl ether (×3). The combined extracts were washed with water and then brine, dried over Na_2SO_4, and concentrated under vacuum to give **8** as a colorless oil (4.7 mg, 73.4% yield). GLC analysis (TC-Wax (id 0.25 mm×60 m), 140°C, 30 cm/s) of **8** shows two peaks at 46.6 and 48.4 min in a ratio 89.5:10.5. For the major diastereomer of **8**: ^{1}H NMR δ 4.11 (q, $J=7.1$ Hz, 2H), 4.01 (m, 2H), 2.70 (dd, $J=14.7$, 4.4 Hz, 1H), 2.15 (dd, $J=14.7$, 8.8 Hz, 1H), 2.09 (m, 1H), 1.99 (brd, $J=9.3$ Hz, 1H), 1.66–1.28 (m, 9H), 1.25 (t, $J=7.1$ Hz, 3H), 1.17 (d, $J=6.1$ Hz, 3H), 1.16 (d, $J=6.3$ Hz, 3H); ^{13}C NMR δ 173.9, 99.5, 64.0, 61.3, 59.8, 43.2, 38.4, 34.5, 33.8, 28.4, 24.1, 23.3, 22.2, 21.6, 14.1; HRMS m/z (M+) calcd for $C_{15}H_{26}O_4$, 270.1831, obsvd 270.1821.

p-Toluenesulfonic acid monohydrate (0.02 equiv.) was added to a stirred solution of **7** (321 mg, 1.19 mmol) in benzene at room temperature. The mixture was stirred for 2.5 h at room temperature and for 3 h at 50°C, poured into a saturated aqueous solution of sodium bicarbonate, and extracted with diethyl ether (×3). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum to give an oil (206.3 mg, 94.1% yield). The oil was purified by preparative GLC (Shimadzu 8A with an NPGS-packed column, 150°C) to give **9** as a colorless oil (112.5 mg, 52.2% yield). The spectra of **9** are identical with those reported in the literature.[9] $[\alpha]_D^{20}=-0.6$ (*c* 2.15, MeOH), (lit. $[\alpha]_D=-5.8$).

4.7. Preparation of 11 by thermolysis of 10

To a stirred solution of **4** (200.8 mg, 0.895 mmol) in diethyl ether was added 1.09 M methyllithium (1.64 ml, 2.0 equiv.) in hexane at −78°C over 2 min. The mixture was stirred for 2 h at −78°C and then for 1.5 h at room temperature. The mixture was poured into ice water, and extracted with dichloromethane (×3). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum to give an oil. The oil was purified by silica gel chromatography (elution with 40% ethyl acetate in hexane) to give **10** as a colorless oil (167.2 mg, 72.9% yield). $[\alpha]_D^{20}=-38.8$ (*c* 1.0, $CHCl_3$); IR (neat) 3375 cm^{-1}; ^{1}H NMR δ 4.01 (m, 1H), 3.87 (m, 1H), 2.00–1.88 (m, 3H), 1.63–1.49 (m, 4H), 1.44–1.08 (m, 4H), 1.34 (s, 3H), 1.27 (d, $J=6.3$ Hz, 3H), 1.23 (s, 3H), 1.14 (d, $J=6.3$ Hz, 3H), 0.55 (d, $J=6.8$ Hz, 1H); ^{13}C NMR δ 71.0, 69.3, 64.1, 63.5, 46.1, 38.5, 31.9, 30.9, 30.2, 23.9, 23.8, 21.8, 21.5, 21.0, 18.2; HRMS m/z (M+) calcd for $C_{15}H_{28}O_3$, 256.2038, obsvd 256.2013.

A solution of **10** (5.8 mg, 0.023 mmol) in hexamethylphosphonamide (2 ml) was stirred for 18 h at 180°C. The mixture was cooled to room temperature, poured into water, and extracted with diethyl ether (×3). The combined extracts were washed with water and then brine, dried over Na_2SO_4, and concentrated under vacuum to give a brown oil (7.1 mg). The oil was purified by silica gel chromatography (elution with 20% ethyl acetate in hexane) to give **11** as a colorless oil (4.6 mg, 83.6% yield). GLC analysis (OV-1, id 0.25 mm×30 m, 110°C, 30 cm/s) of **11** shows two separated peaks in

a ratio of 98.8:1.2. $[\alpha]_D^{20} = -24.6$ (c 1.10, $CHCl_3$); IR (neat) 2970, 1450, and 990 cm^{-1}; ^1H NMR δ 5.29 (dd, $J = 9.3$, 1.5 Hz, 1H), 4.06 (m, 1H), 3.92 (m, 1H), 2.39 (ddd, $J = 14.6$, 9.3, 4.9 Hz, 1H), 1.99 (dm, $J = 12.7$ Hz, 1H), 1.69 (s, 3H), 1.63 (d, $J = 1.5$ Hz, 3H), 1.58–1.20 (m, 9H), 1.17 (d, $J = 6.3$ Hz, 3H), 1.06 (d, $J = 6.3$ Hz, 3H); HRMS m/z (M+) calcd for $C_{15}H_{26}O_2$, 238.1934, obsvd 238.1931.

4.8. Preparation of analogues substrates 12–19

Two series of substrates, **12–14** and **15–19** were prepared according to the procedure established for **4**. That involves formation of an acetal (**12A–19A**) from a ketone and a chiral diol, isomerization to an enol ether (**12B–19B**), formation of an acetoacetate ester (**12C–19C**), and introduction of a diazo group to give **12–19**.

4.8.1. Preparation of 12. A solution of cyclohexanone (9.81 g) and 1,3-butanediol (9.91 g) in benzene (200 ml) was heated in the presence of pyridinium *p*-toluenesulfonate (100 mg) using a Dean–Stark apparatus (8.5 h). Concentration and silica gel chromatography (elution with 3% ethyl acetate in hexane) afforded 18.5 g of **12A** as a colorless oil (100%). **12A**: ^1H NMR δ 3.91 (m, 1H), 3.85 (td, $J = 12.4$, 2.8 Hz, 1H), 3.67 (dd, $J = 11.7$, 4.8 Hz, 1H), 1.84–1.75 (m, 2H), 1.50–1.43 (m, 5H), 1.37–1.27 (m, 5H), 1.05 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR δ 128.1, 98.0, 63.8, 59.0, 38.7, 33.0, 27.9, 25.7, 22.4, 22.3. Anal. calcd for $C_{10}H_{18}O_2$, C, 70.55; H, 10.66; obsvd: C, 70.48; H, 10.37.

To a stirred solution of **12A** (5.00 g) in dichloromethane (150 ml), triisobutylaluminum in hexane (138 ml, 0.95 M, 4.5 equiv.) was added dropwise over 10 min at 0°C. The reaction mixture was stirred for further 5 h, poured into a cold 1 M NaOH solution (750 ml) and extracted with dichloromethane (×2). The combined extracts were washed with water, dried over K_2CO_3, and evaporated under vacuum to give **12B** as a colorless oil (4.90 g, 98.0% yield crude). Diketene (2.66 g, 1.15 equiv.) was added to a stirred solution of **12B** (5.0 g, 0.030 mol) and triethylamine (1.67 ml, 0.4 equiv.) in dichloromethane (150 ml) at room temperature. The reaction mixture was stirred for 4 h, poured into water, and extracted with dichloromethane (×3). The combined extracts were washed with water (×2) and then brine (×2), dried ($MgSO_4$), and concentrated under vacuum to give a yellow oil (7.01 g). The oil was purified by silica gel chromatography (elution with 25% ethyl acetate in hexane) to give **12C** as a colorless oil (6.62 g, 75.7% yield). **12C**: IR (neat) 1750, 1730, and 1670 cm^{-1}; ^1H NMR δ 4.60 (t like, $J = 2.9$ Hz, 1H), 4.22–4.12 (m, 3H), 3.43 (s, 2H), 2.25 (s, 3H), 2.04–1.79 (m, 6H), 1.67–1.61 (m, 2H), 1.54–1.48 (m, 2H), 1.20 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR δ 199.6, 166.5, 152.3, 95.0, 67.4, 61.9, 49.6, 35.1, 29.6, 27.8, 23.3, 22.7, 22.4, 19.3; HRMS m/z (M+) calcd for $C_{14}H_{22}O_4$, 254.1518, obsvd 254.1498.

To a stirred solution of **12C** (3.00 g, 11.2 mmol) and toluenesulfonyl azide (2.60 g, 1.1 equiv.) in acetonitrile (60 ml), triethylamine (6.2 ml, 3.7 equiv.) was added dropwise at 0°C in 5 min. After stirring for 2 h, the reaction mixture was allowed to warm up to room temperature, stirred for further 4 h, and then treated with 1 M NaOH aq. (210 ml). The mixture was stirred for 11 h, and extracted with dichloromethane (100 ml×4). The combined extracts were washed with 1 M NaOH (200 ml×2), dried over Na_2SO_4, and concentrated under vacuum to give a yellow oil (2.54 g). The oil was purified using a basic alumina column (elution with 3% ethyl acetate in hexane) to give **12** as a yellow oil (2.00 g, 69.9% yield). **12**: IR (neat) 2100 and 1700 cm^{-1}; ^1H NMR δ 4.71 (s, 1H), 4.60 (t like, $J = 3.9$ Hz, 1H), 4.25–4.12 (m, 3H), 2.06–1.76 (m, 6H), 1.67–1.61 (m, 2H), 1.54–1.48 (m, 2H), 1.20 (d, $J = 5.9$ Hz, 3H); ^{13}C NMR δ 166.3, 152.5, 67.7, 61.7, 45.8, 35.5, 27.9, 23.5, 22.8, 22.6, 19.6; HRMS m/z (M+−N_2) calcd for $C_{12}H_{18}O_3$, 210.1256, obsvd 210.1222.

4.8.2. Preparation of 13. Treatment of **12A** (10 g) with pyridinium perbromide (29.01 g) in dry THF (200 ml) at −78°C, and extraction after warming up to room temperature gave an isomeric mixture of an α-bromoacetal (19.77 g, 135% crude yield). To a solution of naphthalene (1 g) in THF (25 ml), lithium (0.88 g) was added at room temperature. A solution of the crude α-bromoacetal (8 g) was added dropwise to this under ultrasonic irradiation, in keeping the reaction media blue. Extraction and silica gel column chromatography afforded a regio-isomeric mixture in a 1:1 ratio of the enol ethers **12B** and **13B** as a colorless oil (2.72 g, 50.2% for two steps). To a stirred solution of the oil and triethylamine (0.88 ml, 0.4 equiv.) in dichloromethane (150 ml) was added diketene (1.6 g, 1.2 equiv.) at room temperature. The mixture was stirred for 3 h, poured into water, and extracted with dichloromethane (×3). The combined extracts were washed with water (×2) and then brine (×2), dried ($MgSO_4$), and concentrated under vacuum to give a yellow oil. The oil was purified by silica gel chromatography (10% ethyl acetate in hexane) to give two isomers, **13C** in 20.7% and **12C** 14.2% yield. **13C**: IR (neat) 1750, 1730, and 1670 cm^{-1}; ^1H NMR δ 5.07–5.00 (m, 2H), 4.51 (s, 1H), 4.16 (m, 1H), 3.35 (s, 2H), 2.27 (s, 3H), 1.97–1.91 (m, 4H), 1.70–1.42 (m, 6H), 1.22 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR δ 204.0, 166.5, 77.2, 70.2, 62.3, 55.7, 50.1, 42.0, 35.4, 30.2, 27.9, 23.6, 23.1, 20.0; HRMS m/z (M+) calcd for $C_{14}H_{22}O_4$, 254.1518, obsvd 254.1498.

To a stirred solution of **13C** (225 mg, 0.888 mmol) and *p*-toluenesulfonyl azide (228 mg, 1.3 equiv.) in acetonitrile (6 ml), triethylamine (0.46 ml, 3.7 equiv.) was added dropwise at 0°C in 5 min. After stirring for 2 h, the reaction mixture was allowed to warm up to room temperature, stirred for 4 h, and then treated with 1 M NaOH (10 ml). The mixture was stirred for 11 h, and then extracted with dichloromethane (10 ml×4). The combined extracts were washed with 1 M NaOH (25 ml×2) and then water (20 ml×2), dried over Na_2SO_4, and concentrated under vacuum to give a yellow oil. The oil was purified with a basic alumina column (elution with 3% ethyl acetate in hexane) to give **13** as a yellow oil (177 mg, 83.6% yield). IR (neat) 2100 and

1700 cm^{-1}; ^{1}H NMR δ 5.12 (m, 1H), 4.69 (s, 1H), 4.56 (t, J=2.4 Hz, 1H), 3.64 (t, J=6.8 Hz, 2H), 2.03–1.92 (m, 3H), 1.91–1.81 (m, 3H), 1.64 (m, 1H), 1.51 (m, 1H), 1.28 (d, J=4.9 Hz, 3H); ^{13}C NMR δ 152.5, 95.1, 69.3, 67.8, 42.5, 31.9, 28.2, 25.4, 23.8, 23.1, 20.7, 19.8; HRMS m/z (M+–N_2) calcd for $C_{12}H_{18}O_3$, 210.1256, obsvd 210.1253.

4.8.3. Preparation of 14. A solution of cyclohexanone (9.81 g) and 2-methyl-1,3-propanediol (9.91 g) in benzene (200 ml) was heated in the presence of pyridinium *p*-toluenesulfonate (100 mg) using a Dean–Stark apparatus (8.5 h). Concentration and silica gel chromatography (elution with 3% ethyl acetate in hexane) afforded 18.0 g of **14A** as a pale yellow oil (100%). **14A**: ^{1}H NMR δ 3.62 (dd, J=12.4, 4.8 Hz, 2H), 3.37 (t, J=9.6 Hz, 2H), 1.82 (m, 1H), 1.69 (brs, 2H), 1.48 (dd, J=12.4, 5.5 Hz, 2H), 1.40 (dt, J=12.4, 5.5 Hz, 2H), 1.32 (dt, J=12.4, 5.5 Hz, 2H), 1.25 (dd, J=12.4, 6.9 Hz, 2H), 0.65 (d, J=6.9 Hz, 3H); ^{13}C NMR δ 128.1, 97.3, 65.1, 36.5, 20.2, 28.7, 25.6, 22.4, 22.2, 13.1. Anal. calcd for $C_{10}H_{18}O_2$, C, 70.55; H, 10.66; obsvd: C, 70.00; H, 11.50.

To a stirred solution of **14A** (10.5 g) in dichloromethane (300 ml), a solution of triisobutylaluminum in hexane (294 ml, 0.95 M, 4.5 equiv.) was added dropwise at 0°C in 15 min. The reaction mixture was stirred for 5 h, poured into a cold aq. solution of NaOH (1 M, 750 ml) and extracted with dichloromethane. The extract was washed with water, dried over K_2CO_3, and concentrated under vacuum to give **14B** as a colorless oil (10.3 g, 98.1% crude yield), which was directly used for the next step.

Diketene (2.94 g, 1.15 equiv.) was added to a stirred solution of **14B** (6 g, 0.035 mol) and triethylamine (1.9 ml, 0.39 equiv.) in dichloromethane (10 ml) at room temperature. The reaction mixture was stirred for 9 h, poured into water, and extracted with dichloromethane (×3). The combined extracts were washed with water (×2) and then brine (×2), dried ($MgSO_4$), and concentrated under vacuum to give a yellow oil (9.3 g). The oil was purified by silica gel chromatography (elution with 15% ethyl acetate in hexane) to give **14C** as a colorless oil (6.79 g, 68.7% yield). IR (neat) 1750, 1730, and 1670 cm^{-1}; ^{1}H NMR δ 4.54 (t, J=2.4 Hz, 1H), 4.12 (dd, J=10.7, 5.9 Hz, 1H), 4.06 (dd, J=10.7, 5.9 Hz, 1H), 3.50 (d, J=5.9 Hz, 2H), 3.43 (s, 2H), 2.23 (s, 3H), 2.16 (m, 1H), 2.01–1.98 (m, 4H), 1.64–1.61 (m, 2H), 1.51–1.48 (m, 2H), 0.96 (d, J=6.8 Hz, 3H); ^{13}C NMR δ 199.8, 175.1, 166.7, 154.2, 93.6, 67.4, 67.1, 49.8, 32.7, 29.8, 27.5, 23.3, 22.7, 13.8. HRMS m/z (M+) calcd for $C_{14}H_{22}O_4$, 254.1518, obsvd 254.1551.

To a stirred solution of **14C** (3.00 g, 0.012 mol) and *p*-toluenesulfonyl azide (2.60 g, 1.1 equiv.) in dry acetonitrile (60 ml), triethylamine (6.2 ml, 3.7 equiv.) was added dropwise at 0°C in 5 min. After stirring for 30 min, the reaction mixture was allowed to warm to room temperature, stirred for an additional 4 h, and then treated with 1 M NaOH (210 ml). The mixture was stirred 8 h, and extracted with dichloromethane (×2). The combined extracts were washed with 1 M aq. NaOH solution and then water, dried over K_2CO_3, and concentrated under vacuum to give a yellow oil (2.39 g, 83.6% crude). The oil was purified on a basic alumina column (elution with 3% ethyl acetate in hexane) to give **14** as a yellow oil (1.85 g, 64.7% yield). IR (neat) 2110 and 1700 cm^{-1}; ^{1}H NMR δ 4.69 (s, 1H), 4.51 (s, 1H), 4.06 (dd, J=10.7, 5.9 Hz, 2H), 3.50–3.42 (m, 2H), 2.13–2.08 (m, 1H), 2.00–1.90 (m, 4H), 1.60–1.57 (m, 2H), 1.47–1.44 (m, 2H), 0.92 (d, J=6.8 Hz, 3H); ^{13}C NMR δ 168.3, 154.4, 93.6, 67.3, 66.7, 45.9, 33.0, 27.6, 23.4, 22.8, 22.7, 13.9; HRMS m/z (M+–N_2) calcd for $C_{12}H_{18}O_3$, 210.1256, obsvd 210.1235.

4.9. Synthesis of 15–19

4.9.1. Preparation of enol ethers 15B–19B. Acetals **15A**–**17A** were prepared from (2*R*,4*R*)-2,4-pentanediol and ketones, and were converted to enol ethers **15B**–**17B** by the reported method.[5] Acetal **18A** was prepared using 2-methoxypropene (2 equiv.) instead of acetone without azeotropic dehydration. Acetal **19A** and enol ethers **18B** and **19B** were prepared according to the reported method.[5] **18A**: $[\alpha]_D^{20}$=–44.7 (*c* 1.07, CH_2Cl_2); IR (neat) 2980, 1380 and 1227 cm^{-1}; ^{1}H NMR δ 3.94 (m, 6H), 1.56 (t, J=7.6 Hz, 2H), 1.34 (s, 6H), 1.16 (d, J=6.2 Hz, 6H); ^{13}C NMR δ 99.8, 62.5, 41.4, 25.0, 21.6. Anal. calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18; obsvd: C, 66.59; H, 11.20. **19A**: $[\alpha]_D^{20}$=+3.9 (*c* 0.99, CH_2Cl_2); IR (neat) 2980, 1380 and 1270 cm^{-1}; ^{1}H NMR δ 7.52 (dd, J=8.3, 1.5 Hz, 2H), 7.33 (dd, J=6.1, 1.5 Hz, 2H), 7.26 (t-like, J=1.5 Hz, 1H), 4.19 (m, 1H), 3.68 (m, 1H), 1.64 (ddd, J=12.8, 8.6, 5.6 Hz, 1H), 1.53 (s, 3H), 1.52 (ddd, J=12.8, 9.8, 6.1 Hz, 1H), 1.23 (d, J=6.3 Hz, 3H), 1.21 (d, J=6.3 Hz, 3H); ^{13}C NMR δ 144.7, 127.8, 127.2, 125.5, 100.5, 63.6, 63.1, 40.5, 28.7, 21.50, 21.46; HRMS m/z (M+) calcd for $C_{13}H_{18}O_2$, 206.1307, obsvd 206.1287. **18B**: $[\alpha]_D^{20}$=–41.5 (*c* 1.08, CH_2Cl_2); IR (neat) 3375, 2696 and 1280 cm^{-1}; ^{1}H NMR δ 4.33 (m, 1H), 3.98 (m, 1H), 3.87 (s, 1H), 3.85 (s, 1H), 2.28 (m, 1H, OH), 1.75 (s, 3H), 1.63 (m, 2H), 1.20 (d, J=6.2 Hz, 3H), 1.15 (dm, J=6.2 Hz, 3H); ^{13}C NMR δ 158.0, 82.1, 69.8, 64.6, 44.9, 23.6, 21.5, 19.0; HRMS m/z (M+) calcd for $C_8H_{16}O_2$, 144.1150, obsvd 144.1131. **19B**: $[\alpha]_D^{20}$=–71.7 (*c* 1.03, CH_2Cl_2); IR (neat) 3390, 2969, 1643 cm^{-1}; ^{1}H NMR δ 7.52 (dd, J=8.3, 1.5 Hz, 2H), 7.28–7.14 (m, 1H), 4.79 (d, J=2.4 Hz, 1H), 4.54 (m, 1H), 4.31 (d, J=2.4 Hz, 1H), 3.90 (m, 1H), 1.68 (ddd, J=14.1, 8.6, 2.9 Hz, 1H), 1.49 (ddd, J=14.1, 9.5, 3.4 Hz, 1H), 1.20 (d, J=6.1 Hz, 3H), 1.00 (d, J=6.1 Hz, 3H); ^{13}C NMR δ 158.3, 137.0, 128.4, 125.5, 83.7, 70.4, 64.7, 45.5, 23.9, 19.1; HRMS m/z (M+) calcd for $C_{13}H_{18}O_2$, 206.1307, obsvd 206.1279.

4.9.2. Conversion of 15B–19B to 15C–19C. 4-Dimethylaminopyridine (0.2 equiv.) was added to a stirred solution of **B** (3.0 g) and methyl acetoacetate (1.7 equiv.) in benzene (120 ml) at room temperature. The mixture was stirred under reflux for 48–72 h and concentrated under vacuum to give a brown oil. The oil was purified by silica gel chromatography (elution with 20% ethyl acetate in hexane) to give **C**. **15C**: colorless prisms (72.5% yield); mp 30.5–31.5°C; $[\alpha]_D^{20}$=–42.8

(c 0.99, CH_2Cl_2); IR (neat) 1750, 1720 and 1650 cm^{-1}; ^1H NMR δ 5.11 (m, 1H), 4.37 (t, $J=3.5$ Hz, 1H), 4.10 (m, 1H), 3.40 (s, 2H), 2.35–2.21 (m, 5H), 1.98–1.94 (m, 2H), 1.86–1.75 (m, 4H), 1.26 (d, $J=6.1$ Hz, 3H), 1.24 (d, $J=6.1$ Hz, 3H); MS m/z (M+) calcd for $C_{14}H_{22}O_4$, 254.1518, obsvd 254.1521. **16C**: colorless oil (77.3% yield); $[\alpha]_D^{20}=-42.8$ (c 1.02, CH_2Cl_2); IR (neat) 1750, 1730 and 1660 cm^{-1}; ^1H NMR δ 5.11 (m, 1H), 4.69 (t, $J=6.8$ Hz, 1H), 3.98 (m, 1H), 3.40 (s, 2H), 2.26 (s, 3H), 2.20–2.17 (m, 2H), 2.04–1.99 (m, 2H), 1.78–1.40 (m, 8H), 1.26 (d, $J=6.4$ Hz, 3H), 1.24 (d, $J=6.1$ Hz, 3H); MS m/z (M+) calcd for $C_{16}H_{26}O_4$, 282.1832, obsvd 282.1876. **17C**: colorless oil (90.0% yield); $[\alpha]_D^{20}=-40.1$ (c 1.04, CH_2Cl_2); IR (neat) 1750, 1720 and 1660 cm^{-1}; ^1H NMR δ 5.09 (m, 1H), 4.44 (t, $J=8.0$ Hz, 1H), 4.10 (m, 1H), 3.40 (s, 2H), 2.42–2.39 (m, 2H), 2.25 (s, 3H), 2.16 (t, $J=6.1$ Hz, 1H), 2.05–2.04 (m, 2H), 1.87 (m, 1H), 1.77–1.17 (m, 8H), 1.27 (d, $J=6.1$ Hz, 3H), 1.17 (d, $J=6.1$ Hz, 3H); MS m/z (M+) calcd for $C_{17}H_{28}O_4$, 296.1988, obsvd 296.2013. **18C**: colorless oil (18.5% yield); $[\alpha]_D^{20}=-35.0$ (c 0.51, CH_2Cl_2); IR (neat) 1740, 1720 and 1660 cm^{-1}; ^1H NMR δ 5.15 (m, 1H), 4.14 (m, 1H), 3.85 (d, $J=0.7$ Hz, 1H), 3.79 (d, $J=1.7$ Hz, 1H), 3.40 (s, 2H), 2.25 (s, 3H), 1.79–1.55 (m, 5H), 1.26 (d, $J=6.4$ Hz, 3H), 1.21 (d, $J=5.9$ Hz, 3H); ^{13}C NMR δ 2000.5, 166.5, 158.3, 81.6, 69.3, 68.5, 50.6, 43.0, 30.0, 21.3, 19.3; MS m/z (M+) calcd for $C_{12}H_{20}O_4$, 228.1362, obsvd 228.1320. **19C**: colorless oil (84.6% yield); $[\alpha]_D^{20}=-51.0$ (c 0.96, CH_2Cl_2); IR (neat) 1714, 1643 cm^{-1}; ^1H NMR δ 7.57 (m, 2H), 7.31 (m, 3H), 5.24 (m, 1H), 4.66 (d, $J=2.7$ Hz, 1H), 4.37 (m, 1H), 4.20 (d, $J=2.7$ Hz, 1H), 3.38 (s, 2H), 2.21 (s, 3H), 2.00–1.86 (m, 2H), 132 (d, $J=6.1$ Hz, 3H), 1.31 (d, $J=6.4$ Hz, 3H); ^{13}C NMR δ 200.6, 166.5, 158.3, 137.0, 128.4, 128.1, 125.6, 83.3, 69.5, 69.2, 50.4, 43.0, 30.1, 20.5, 19.3; MS m/z (M+) calcd for $C_{17}H_{22}O_4$, 290.1518, obsvd 290.1559.

4.9.3. Conversion of 15C–19C to 15–19. To a solution of **C** (1.5 g, 1.0 equiv.), p-toluenesulfonyl azide (1.5 equiv.) in acetonitrile (30 ml), triethylamine (3.0 equiv.) was added dropwise at 0°C. After stirring for 2–3 h, the mixture was added to 1 M NaOH (15 ml). After 15–20 h of stirring, the mixture was extracted with diethyl ether (50 ml, 3×) and washed with water (100 ml). Drying over Na_2SO_4, concentration, and column chromatography on silica gel (elution with 20% ethyl acetate in hexane) afforded 0.5–1.7 g of the diazo ester as a deep yellow oil. **15**: yellow oil (65.8% yield); $[\alpha]_D^{20}=-74.9$ (c 1.04, CH_2Cl_2); IR (neat) 2110 and 1700 cm^{-1}; ^1H NMR δ 5.10 (m, 1H), 4.69 (s, 1H), 4.37 (s, 1H), 4.08 (m, 1H), 2.36–2.21 (m, 4H), 1.87–1.71 (m, 4H), 1.27 (d, $J=6.3$ Hz, 3H), 1.24 (d, $J=6.1$ Hz, 3H); MS m/z (M+−N_2) calcd for $C_{13}H_{18}O_3$, 210.1256, obsvd 210.1297. **16**: yellow oil (71.2% yield); $[\alpha]_D^{20}=-69.0$ (c 1.03, CH_2Cl_2); IR (neat) 2120 and 1700 cm^{-1}; ^1H NMR δ 5.09 (m, 1H), 4.70 (t, $J=6.8$ Hz, 1H), 4.68 (s, 1H), 4.00 (m, 1H), 2.21–2.18 (m, 2H), 2.03 (dd, $J=11.0$, 6.8 Hz, 1H), 1.80–1.60 (m, 4H), 1.55–1.39 (m, 4H), 1.26 (d, $J=6.4$ Hz, 3H), 1.17 (d, $J=6.1$ Hz, 3H); MS m/z (M+−N_2) calcd for $C_{14}H_{22}O_3$, 238.1569, obsvd 238.1602. **17**: yellow oil (66.0% yield); $[\alpha]_D^{20}=-71.4$ (c 1.01, CH_2Cl_2); IR (neat) 2120 and 1700 cm^{-1}; ^1H NMR δ 5.09 (m, 1H), 4.69 (s, 1H), 4.44 (t, $J=8.3$ Hz, 1H), 4.09 (m, 1H), 2.21–2.15 (m, 2H), 2.05–1.98 (m, 2H), 1.76–1.65 (m, 4H), 1.55–1.39 (m, 4H), 1.27 (d, $J=6.1$ Hz, 3H), 1.18 (d, $J=6.1$ Hz, 3H); MS m/z (M+−N_2) calcd for $C_{15}H_{24}O_3$, 252.1725, obsvd 252.1696. **18**: yellow oil (45.6% yield); $[\alpha]_D^{20}=-57.9$ (c 1.05, CH_2Cl_2); IR (neat) 2109 and 1695 cm^{-1}; ^1H NMR δ 5.10 (m, 1H), 4.69 (s, 1H), 4.13 (m, 1H), 3.85 (d, $J=1.6$ Hz, 1H), 3.78 (d, $J=1.6$ Hz, 1H), 1.83–1.71 (m, 2H), 1.77 (s, 3H), 1.27 (d, $J=6.4$, 3H), 1.22 (d, $J=6.1$ Hz, 3H); ^{13}C NMR δ 166.3, 158.1, 81.5, 68.9, 68.7, 46.2, 43.1, 21.3, 20.7. 19.3; MS m/z (M+−N_2) calcd for $C_{10}H_{16}O_3$, 212.1161, obsvd 212.1158. **19**: yellow oil (26.6% yield); $[\alpha]_D^{20}=-19.3$ (c 1.06, CH_2Cl_2); IR (neat) 2100 and 1690 cm^{-1}; ^1H NMR δ 7.58 (ddm, $J=8.3$, 1.5 Hz, 2H), 7.32 (m, 3H), 5.21 (m, 1H), 4.67 (s, 1H), 4.66 (d, $J=2.7$ Hz, 1H), 4.35 (m, 1H), 4.19 (d, $J=2.7$ Hz, 1H), 1.98 (ddd, $J=14.4$, 8.3, 4.2 Hz, 1H), 1.88 (ddd, $J=14.4$, 8.8, 4.2 Hz, 1H), 1.32 (d, $J=5.9$ Hz, 3H), 1.31 (d, $J=6.4$ Hz, 3H); ^{13}C NMR δ 160.3, 158.3, 137.0, 128.3, 125.6, 69.5, 69.0, 46.2, 43.1, 20.4, 19.4; MS m/z (M+−N_2) calcd for $C_{15}H_{18}O_3$, 246.1256, obsvd 246.1222.

4.10. Metal-catalyzed reaction of 12–19 to give cyclopropanes 12D–19D

4.10.1. Intramolecular cycloaddition of 12–14. The diazo ester substrate was dissolved in dichloromethane as a ca. 1 M solution, and a catalytic amount of $Rh_2(OAc)_4$ was added at room temperature under stirring. After 30–60 min, the reaction mixture was concentrated and purified by silica gel column chromatography (elution with 10% ethyl acetate in hexane) to give cycloadduct **D**. Stereochemistries of the major diastereomer were determined by NOE experiments. Diastereomeric ratios of **12D** and **13D** were determined by GLC after treatments by ethanolysis and protection with TBS group under the conditions converted **4** to **6**. Diastereomeric ratio of **14D** was determined by ^1H NMR. **12D**: mp 62–63°C; IR (KBr) 1730 cm^{-1}; ^1H NMR δ 4.56 (ddd, $J=12.4$, 12.4, 3.4 Hz, 1H, H-5), 4.13 (ddd, $J=12.4$, 6.2, 2.1 Hz, 1H, H-5′), 3.36 (dqd, $J=12.4$, 6.2, 2.1 Hz, 1H, H-3), 2.09 (m, 1H), 2.03 (m, 1H), 1.97–1.85 (m, 2H), 1.77 (ddd, $J=7.6$, 7.6, 1.4 Hz, 1H, H-9), 1.70–1.59 (m, 2H), 1.55 (m, 1H), 1.34 (d, $J=7.6$ Hz, 1H, H-8), 1.33–1.26 (m, 2H), 1.12 (m, 1H), 1.13 (d, $J=6.2$ Hz, 1H); NOE enhancement between H-3 and H-9, 9%; ^{13}C NMR δ 174.2, 65.2, 64.2, 63.5, 39.9, 91.9, 29.5, 23.0, 22.0, 21.3, 21.13, 21.09; HRMS m/z (M+) calcd for $C_{12}H_{18}O_3$, 210.1256, obsvd 210.1264; GLC after the conversion (TC-1, 0.25 mm i.d.×25 m, 150°C, 29 cm/s) retention times, 81.0 (major) and 83.0 min. **13D**: mp 98.5–99.0°C; IR (KBr) 1711 cm^{-1}; ^1H NMR δ 5.07 (m, 1H, H-5), 3.83 (ddd, $J=13.1$, 3.4, 3.4 Hz, 1H, H-3), 3.56 (m, 1H, H-3′), 2.28 (m, 1H), 2.23 (ddd, $J=13.7$, 5.5, 5.5 Hz, 1H), 2.03 (ddd, $J=13.7$, 13.7, 5.5 Hz, 1H), 1.88 (m, 1H), 1.66 (m, 1H), 1.56–1.42 (m, 2H), 1.48 (d, $J=6.2$ Hz, 1H, H-8), 1.32 (d, $J=6.2$ Hz, 3H), 1.26–1.22 (m, 2H), 1.08 (m, 1H); NOE enhancement between H5 and H-8, 1.5%; ^{13}C NMR δ 177.0, 76.4, 71.2, 65.8, 40.9, 33.3, 29.6, 28.8, 23.6, 21.8, 20.9, 20.8; HRMS m/z (M+) calcd for $C_{12}H_{18}O_3$, 210.1256, obsvd 210.1264; GLC after the conversion (TC-1, 0.25 mm i.d.×25 m, 150°C, 29 cm/s) retention time, 84.2 min. **14D** (as a

diastereomeric mixture): ^{1}H NMR δ 4.85 (dd, J=11.7, 3.4 Hz, 0.65H, H-5), 4.47 (dd, J=11.7, 10.7 Hz, 0.35H, H-5), 4.07 (m, 0.35H, H-5′), 3.93 (ddd, J=11.7, 3.4, 1.4 Hz, 0.65H, H-5′), 3.76 (dd, J=9.5, 2.1 Hz, 0.65H, H-3), 3.68 (m, 0.35H, H-3), 3.56 (m, 0.65H, H-3′), 3.35 (ddd, J=12.4, 11.0, 0.4 Hz, 0.35H, H-3′), 2.27–2.20 (m, 1H), 2.19–2.13 (m, 1H, H-9), 2.09–1.99 (m, 1H), 1.97–1.87 (m, 2H), 1.57–1.45 (m, 2H), 1.47 (d, J=6.2 Hz, 0.35H, H-8), 1.44 (d, J=6.2 Hz, 0.65H, H-8), 1.33–1.20 (m, 2H), 1.13–1.04 (m, 1H), 1.09 (d, J=7.6 Hz, 1.95H), 0.70 (d, J=7.6 Hz, 1.05H); NOE enhancement between H-5 and H-8 of the major diastereomer, 1%; ^{13}C NMR (for the major isomer) δ 176.8, 72.5, 69.60, 69.3, 36.6, 32.5, 29.3, 27.4, 23.27, 20.99, 20.7, 15.2; ^{13}C NMR (for the minor isomer) δ 176.5, 73.5, 71.6, 69.57, 37.8, 32.8, 29.2, 28.0, 23.31, 20.95, 20.8, 13; HRMS m/z (M+) calcd for $C_{12}H_{18}O_3$, 210.1256, obsvd 210.1219.

4.10.2. Intramolecular cycloaddition of 15–19. A solution of the substrate (100–200 mg, 1.0 equiv.) in dry benzene (2–4 ml) was heated until reflux in the presence of dry $CuSO_4$ (0.02 equiv.). After 2 h, the mixture was allowed to cool to room temperature, and concentrated under vacuum to give a pale yellow oil. The oil was purified by silica gel chromatography (elution with 15% ethyl acetate in hexane) to give a stereochemically pure intramolecular cycloadduct **D**. Stereochemical purities of **D** were determined by the GLC analysis used for **4**. **15D**: colorless prisms (55.2% yield); mp 65.5–66.5°C; $[\alpha]_D^{20}=-58.7$ (c 0.95, MeOH); IR (KBr) 1730 cm^{-1}; ^{1}H NMR δ 4.95 (m, 1H), 3.35 (m, 1H), 2.11–1.91 (m, 4H), 1.83–1.61 (m, 4H), 1.58 (d, J=4.2 Hz, 1H), 1.34 (d, J=6.4 Hz, 3H), 1.15 (d, J=6.1 Hz, 3H), 1.10 (m, 1H); ^{13}C NMR δ 173.6, 76.2, 71.8, 67.5, 47.7, 34.3, 26.9, 26.6, 25.8, 22.1, 21.1, 20.0; HRMS m/z (M+) calcd for $C_{12}H_{18}O_3$, 210.1256, obsvd 210.1248. **16D**: colorless prisms (63.5% yield); mp 66.0–67.5°C; $[\alpha]_D^{20}=-14.6$ (c 0.96, MeOH); IR (KBr) 1730 cm^{-1}; ^{1}H NMR δ 4.87 (m, 1H), 3.40 (m, 1H), 2.34 (dd, J=14.4, 7.3 Hz, 2H), 1.79–1.60 (m, 8H), 1.47 (d, J=7.3 Hz, 1H), 1.45–1.17 (m, 5H), 1.35 (d, J=6.1 Hz, 3H), 1.12 (d, J=6.1 Hz, 3H), 1.01 (dd, J=24.4, 10.3 Hz, 1H); ^{13}C NMR δ 173.3, 72.1, 70.0, 64.8, 47.7, 38.3, 35.0, 31.8, 30.8, 28.3, 26.4, 25.6, 22.1, 21.3; HRMS m/z (M+) calcd for $C_{14}H_{22}O_3$, 238.1569, obsvd 238.1589. **17D**: colorless prisms (54.6% yield); mp 94.0–96.0°C; $[\alpha]_D^{20}=+12.6$ (c 0.97, MeOH); IR (KBr) 1710 cm^{-1}; ^{1}H NMR δ 4.85 (m, 1H), 3.44 (m, 1H), 2.23 (dt, J=14.2, 3.4 Hz, 2H), 1.83–1.08 (m, 12H), 1.33 (d, J=6.1 Hz, 3H), 1.21 (td, J=14.2, 3.4 Hz, 1H), 1.12 (d, J=6.1 Hz, 3H), 0.98 (dd, J=12.0, 2.4 Hz, 1H); ^{13}C NMR δ 173.7, 72.0, 68.1, 64.7, 47.7, 34.2, 31.4, 28.5, 27.9, 26.2, 26.1, 25.9, 24.8, 22.1, 21.3; HRMS m/z (M+) calcd for $C_{15}H_{24}O_3$, 252.1726, obsvd 252.1710. **18D**: colorless oil (22.4% yield); $[\alpha]_D^{20}=+19.1$ (c 0.69, CH_2Cl_2); IR (neat) 1729 cm^{-1}; ^{1}H NMR δ 4.89 (m, 1H), 3.28 (m, 1H), 1.77 (m, 1H), 1.65 (m, 1H), 1.52 (dd, J=10.3, 7.6 Hz, 1H), 1.39 (m, 1H), 1.37 (d, J=6.4 Hz, 3H), 1.12 (d, J=6.1 Hz, 3H), 1.10 (m, 1H); ^{13}C NMR 173.0, 72.0, 65.1, 63.0, 47.8, 26.8, 25.7, 21.8, 21.0, 15.1; HRMS m/z (M+) calcd for $C_{10}H_{16}O_3$, 184.1099, obsvd 184.1133. **19D**: colorless oil (39.1% yield); $[\alpha]_D^{20}=+96.2$ (c 0.95, MeOH); IR (neat) 1730 cm^{-1}; ^{1}H NMR δ 7.58–7.26 (m, 5H), 4.93 (m, 1H), 3.76 (m, 1H), 2.06 (dd, J=10.5, 8.3 Hz, 1H), 1.96 (ddd, J=14.3, 10.7, 3.6 Hz, 1H), 1.88 (dd, J=8.3, 7.1 Hz, 1H), 1.73 (m, 1H), 1.66 (dd, J=10.5, 7.1 Hz, 1H), 1.32 (d, J=6.3 Hz, 3H), 1.26 (d, J=6.3 Hz, 3H); ^{13}C NMR δ 172.3, 142.3, 128.7, 127.4, 124.3, 72.2, 66.9, 66.0, 47.1, 31.4, 22.2, 21.5, 18.8. HRMS m/z (M+) calcd for $C_{15}H_{18}O_3$, 246.1256, obsvd 246.1283.

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