 

# Preparation of Methoxy-Substituted Optically Active 7-Alkoxycarbonylcycloheptatrienes and Their Acid-Promoted Rearrangements

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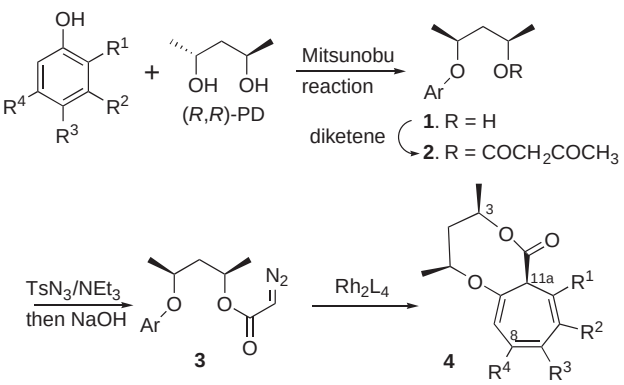
Four optically active cycloheptatriene derivatives carrying a methoxy group(s) at different positions were prepared by the 2,4-pentanediol-tethered Büchner reaction. In addition to the high stereoselectivity, the tether also controlled the regioselectivity in a good-to-high degree. Some of the products are unstable under acidic conditions, resulting in isomerization through a prototropic reaction or aromatization. The Brønsted acid promoted prototropic isomerization by regio- and stereoselective protonation and ensuing deprotonation, while the Lewis acid-catalyzed reaction provided an aromatized product via the norcaradiene tautomer.

Cycloheptatriene and its derivatives can be prepared by carbenoid addition to benzenoid hydrocarbons. A typical example is the Büchner reaction using a diazoacetyl reagent as a source of the carbenoid.[1] Reactions of the Büchner products at the three olefins can give varied compounds under stereocontrol by the 7-substituent, and thus the Büchner products are considered to be good precursors for poly functionalized compounds. Despite the expected usefulness as synthons, an optically active one was not available due to the lack of a proper method of stereoselective formation. In 1998, we reported on an asymmetric synthesis by applying a stereocontrol method using a chiral 1,3-diol tether[2] to the Büchner reaction.[3] A rhodium(II) catalyzed reaction of the substrate **3** carrying aryl ether and diazoacetate ester at each end of the 2,4-pentanediol (PD) tether resulted in a quantitative yield of **4** ($R^{1-4}$ = H), where the stereochemical purity at the new chiral center (11a) was confirmed to be over 99.6% diastereomeric excess (de).[4] In addition to the stereocontrol, the PD tether in the Büchner reaction was found to induce the regioselectivity to a very high degree with **3** having an *ortho*- or *meta*-methyl group ($R^1$ or $R^4$ = Me) at the arene, and in moderate-to-high degree with 3,5-disubstituted **3** ($R^2$, $R^4$ = alkyl, $R^2 \neq R^4$) (Scheme 1).[4,5]

From those studies, optically active **4** having varied substituents at the desired position are expected to be preparable from the corresponding phenol derivatives. Among those **4**, methoxy substituted ones are of interest, since they must be reactive toward electrophilic reagents, and functionalization of the triene part can be achieved under mild conditions. Hence, we studied the reaction of **3** having a methoxy group at different positions, and synthesized optically active methoxy-substituted **4**. During the study, we found that the produced **4**, carrying the 8-methoxy ($R^4$ = OMe) or 10-methoxy ($R^2$ = OMe) group, was unstable under acidic conditions to result in two types of isomerization, depending on the acid employed. We now report on the reaction selectivity for the formation of methoxy-substituted cycloheptatrienes **4** and their isomerization.




Scheme 1.

We would also like to report a correction for one of the isomerization types reported in the preliminary communication.[6]

Substrates **3a–e** were prepared from 2-methoxyphenol, 3-methoxyphenol, 4-methoxyphenol, 3,5-dimethoxyphenol, and 3-methoxy-5-methylphenol, respectively, by the Mitsunobu reaction with (*R*,*R*)-2,4-pentanediol to give one-to-one adducts, followed by a two-step introduction of a diazoacetate ester at the remaining hydroxy group.[4] A solution of **3** in dichloromethane was added dropwise to a stirred dichloromethane solution of a $Rh_2(OAc)_4$ catalyst (3 mol%) at room temperature. This procedure is effective for unsubstituted **3** ($R^{1-4}$ = H) to result in a quantitative yield of **4** without forming dimers at the diazo group. Because all the substrates **3a–e** in the present study have at least two alkoxy substituents on the arene ring, they should be very reactive toward the Büchner reaction, consisting of electrophilic carbenoid addition. However, the reaction of **3a** (= **3**: $R^1$ = OMe) with $Rh_2(OAc)_4$ was sluggish, and gave a mixture of 4–5 compounds (Scheme 2). The reaction was not improved with the $Rh_2(OCOCF_3)_4$ catalyst, which is effective for the reaction of the 2-methyl analogue of **3** ($R^1$ = Me) proceeding at the sterically congested 1,2-posi-

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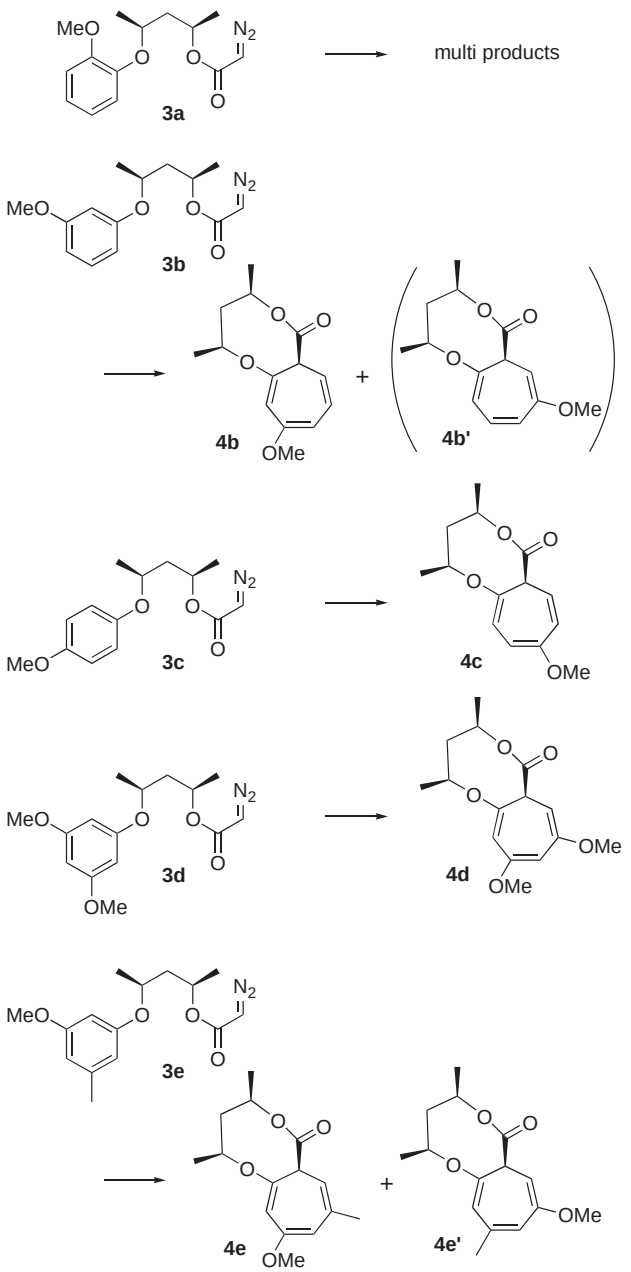



Scheme 2. The PD-tethered Büchner reaction of **3a–e** with a $Rh_2(OAc)_4$ catalyst.

tion.[4] In contrast to the result with **3a**, the reaction of the other substrates, **3b–e**, under the same conditions was smooth, and afforded **4b–e′** quantitatively, except for some carbenoid addition of unpleasant water. However, isolated yields of **4b–e′** from the reaction mixtures were not very high due to their instability, the degree of which largely depends on the compound.

In the case of the reaction of **3b**, the formation of **4b** was regioselective, and its regioisomer **4b′** was not detected at all in the reaction mixture. The strict regiocontrol is attributable to a steric congestion between the methoxy substituent and rhodium carbenoid.[3] The isolation of **4b** could be achieved by a quick manipulation with a short silica-gel column (75% yield), but a longer contact time with silica gel caused the

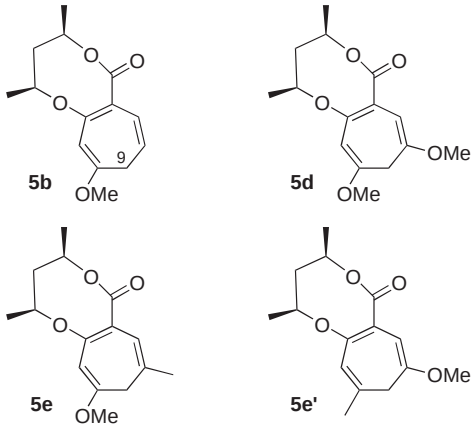


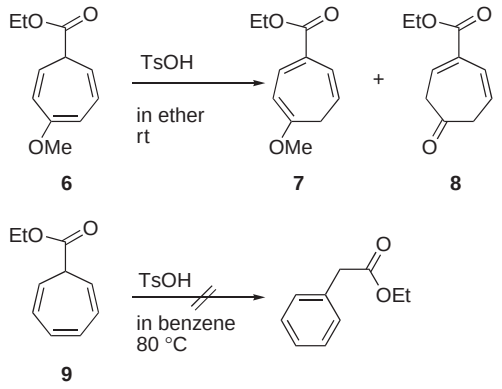

Fig. 1.

decomposition of **4b** to afford **5b** solely (Fig. 1). In contrast, **4c** prepared from **3c** was stable to silica gel, and purification by column chromatography could be performed without any notable problem (70% yield).

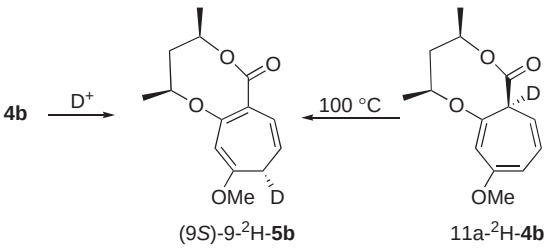
The instability observed for **4b** was more obvious in the case of **4d**, which has an additional methoxy group. After concentration of the product mixture of the rhodium-catalyzed reaction of **3d**, the remaining mixture contained only **5d** (76% yield). The primary product **4d** was detected when the reaction mixture was directly analyzed by NMR during a reaction performed in a deuterated solvent ($CDCl_3$ instead of $CH_2Cl_2$) in the presence of potassium carbonate (>95% pure by $^1$H NMR). In the case of **4e** and its regioisomer **4e′** carrying a methoxy and a methyl group, their stabilities were between **4b** and **4d**. That is, a mixture of **4e** and **4e′** was obtained by the reaction of **3e** in an isomer ratio of **4e**/**4e′** = 3/1, but separation of the isomers by a silica-gel column was not successful, because **5e** and **5e′** were produced during the purification process.

The stereoselectivity of the reaction of **3b–e** was not studied in detail due to the instability of products **4b–e′**. However, judging from the high-resolution $^1$H NMR spectra of the reaction mixtures, the diastereomers of **4b–e′** due to the 11a-stereocenter is less than 1% of **4**, and thus the stereoselectivities are evaluated to be over 99%. The stereochemistry at the 11a-position of **4b–e′** was confirmed to be *S* due to an observation of NOE effects between H-3 and H-11a. The regiochemistry of **4e** and **4e′** was also determined by a NOE measurement. The structures of the secondary products (**5b**, **5d**, **5e**, and **5e′** (Fig. 1)) as well as other new compounds were fully identified by MS and spectroscopic analyses.

The isomerization of **4** to **5** is formally the same as a thermal [1.5] hydride shift, but the thermal rearrangement of **4** does not proceed at room temperature, but requires over 100 °C, as shown below.[7] Therefore, the reaction occurring in the purification step must be promoted by some chemical factor. When *p*-toluenesulfonic acid (TsOH) was added to a dichloromethane solution of **4b**, **5b** was obtained quantitatively (5 h), while the treatment of **4b** with triethylamine in dichloromethane did not show any change at rt (12 h). The same acid treatment of **4c** as well as the unsubstituted **4** ($R^{1-4}$ = H) only showed a very slow reaction, and did not give any clear product. In the case of more reactive **4e** and **4e′**, the transformation




Scheme 3.

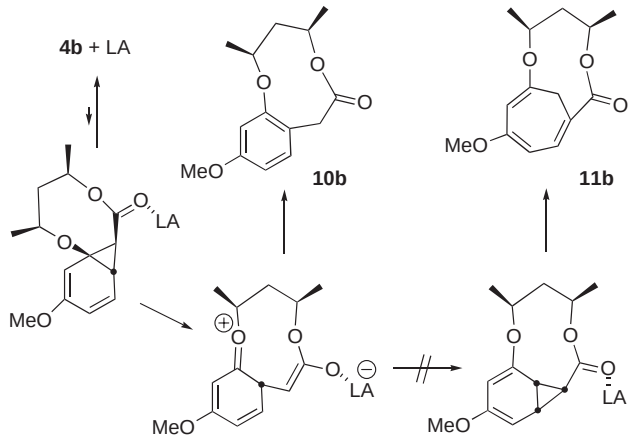



Scheme 4.

to **5e** and **5e′** was achieved by a treatment with silica gel. By this experiment, **4e′** was found to be more reactive than **4e**.

The structural requirement for acid-promoted prototropic isomerization was further investigated. As a more general case, we studied with a simple analogue **6**. By the TsOH treatment in ether, a conversion similar to that of **4b** proceeded to afford **7**[8] (13%) and its keto analog **8** (31%) (Scheme 3). In contrast, **9** was much more stable toward acid, and the TsOH treatment resulted in no reaction, even at higher temperature (80 °C in benzene/24 h), though the reaction of **9** with fluorosulfuric acid is known to give ethyl phenylacetate.[9,10] These results show that the lactone structure in **4** is not indispensable for the isomerization, but the methoxy groups are responsible for both activation of the substrate and the regioselectivity of the reaction. The results also suggest that the acid-promoted or catalyzed prototropic isomerization is general for the methoxy-substituted Büchner products.

The postulated mechanism for the isomerization of **4** consists of protonation at the electron-rich 9-position, followed by deprotonation at the 11a-position, the acidity of which may be enhanced by protonation at the carbonyl oxygen. This mechanism is consistent with the labeled experiment, where the use of TsOD for the reaction of **4b** resulted in regio- and stereoselective mono-deuteration to give (9*S*)-9-$^2$H-**5b** (Scheme 4). The same deuterated compound was also prepared from 11a-$^2$H-**4b** through an internal [1.5] deuterium shift. That is, 11a-$^2$H-**4b** prepared by a base-catalyzed H/D exchange of **4b**, in keeping the stereochemical purity,[11] was heated in benzene to 100 °C in a sealed tube for 1 h. The thermally allowed 1,5-hydride shift occurred regio- and stereospecifically and irreversibly to give (9*S*)-9-$^2$H-**5b** in a quantitative yield.[7] This experiment indicates not only the origin of H-9 in **5b**, but also the stereoselectivity of the protonation step.




Scheme 5.

During the synthesis of **4b**, another secondary product **10b** was accidentally produced. Since the formation of **10b** was inhibited by the addition of a trace amount of amine to **4b** during the purification process, the production of **10b** also seemed to be promoted by acid. When **4b** was treated with a Lewis acid under aprotic conditions, e.g., $ZnI_2$ in ether, $SnCl_4$ in $CH_2Cl_2$, or $Et_2O{\cdot}BF_3$ in ether, **10b** was obtained in a quantitative yield. Because **5b** was almost inert to the same Lewis-acid treatment, **10b** must be produced directly from **4b**. The same rearrangement was also sometimes observed during the isolation process of **4e**. This rearrangement is known for varied Büchner products, proceeding through the norcaradiene tautomer, as shown in Scheme 5, though most examples are promoted by the Brønsted acid (e.g., $CF_3COOH$).[9] In a preliminary communication, we reported that the Lewis-acid treatment of **4b** gave **11b** via a skeletal rearrangement at the norcaradiene tautomer,[6] but now we must revise that the product is not **11b**, but **10b**. The regioisomer **4c** was almost inert to the $Et_2O{\cdot}BF_3$ treatment in ether, but a prolonged treatment resulted in partial decomposition.

In this study, the preparation of four optically active cycloheptatriene analogues was demonstrated. It should be worth noting that the instability of **4** to acid indicates their high reactivity toward electrophilic reagents; further, their addition can be stereoselective, deduced from the results of labeled experiments. In addition, the reactions of **4** to **5** do not simply mean a loss of chirality in **4**, but can be a new preparation method of chiral compounds by stereoselective protonation when another substituent is present at the 9-position. Alternatively, the instability of **4** could be overcome by converting them to other acid-insensitive compounds under basic conditions, such as reduction with lithium tetrahydridoaluminate.[12] Although the aromatization of Büchner products is generally performed by a Brønsted acid, in the case of methoxy-substituted ones, the production of **5** is preferred over that of **10**, and only by avoiding protonation at the electron-rich $\beta$-position of the methoxy substituent, the aromatization to give **10** was achieved.

## Experimental

**General.** All of the products were characterized by NMR spectrometry using a JEOL EXcaliber-400 or ECA-600 spectrometer, and by IR with a JASCO IR-88 spectrophotometer. Optical

rotations were measured with a Perkin-Elmer 243B polarimeter. High-resolution MS was obtained by a JEOL JMS-AX505HF (EI) or a JEOL JMS-T100LC (ESI). Analytical GLC was performed on a Shimadzu GC17A. All solvents were purified by distillation with proper drying agents.

**Preparation of the Substrate 3a–e.** The three-step synthesis of **3** on a gram scale was achieved by applying the reported method.[4] Spectral data for new compounds as well as their yields (in parentheses) are shown below in the order of the (2*R*,4*S*)-4-aryloxy-2-pentanol (**1**), (2*R*,4*S*)-2-acetoacetoxy-4-aryloxypentane (**2**), and (2*R*,4*S*)-4-aryloxy-2-diazoacetoxypentane (**3**). The compounds were isolated as an oil, and were colorless, except for the diazo esters **3** (deep yellow). Data for **1a** (72%): $[\alpha]_D^{20} = +14.3$ (*c* 1.02, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.94–6.84 (m, 4H), 4.46 (m, 1H), 4.03 (m, 1H), 3.85 (s, 3H), 3.73 (brs, 1H), 1.94 (dt like, $J = 14.6$, 9.8 Hz, 1H), 1.70 (ddd, $J = 14.6$, 3.4, 2.0 Hz, 1H), 1.34 (d, $J = 5.9$ Hz, 3H), 1.19 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 150.19, 146.71, 121.84, 120.62, 116.06, 111.62, 67.32, 55.66, 55.61, 45.98, 23.57, 20.58; IR (neat, $cm^{-1}$) 3400, 3019, 1729, 1502, 1216, 1109, 929, 747, 668; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1256. Data for **2a** (78%): $[\alpha]_D^{20} = +22.1$ (*c* 0.96, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.94–6.84 (m, 4H), 5.21 (m, 1H), 4.42 (m, 1H), 3.82 (s, 3H), 3.40 (s, 2H), 2.23 (s, 3H), 2.21 (m, 1H), 1.75 (ddd, $J = 14.2$, 6.3, 4.9 Hz, 1H), 1.31 (d, $J = 5.9$ Hz, 3H), 1.29 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 200.27, 166.37, 150.45, 146.77, 121.61, 120.68, 116.53, 112.15, 72.26, 69.80, 55.73, 50.29, 42.44, 30.04, 20.19, 19.78; IR (neat, $cm^{-1}$) 2979, 1717, 1600, 1493, 1260, 1142, 1040, 758; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1433. Data for **3a** (80%): $[\alpha]_D^{20} = +25.1$ (*c* 1.02, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.94–6.84 (m, 4H), 5.21 (m, 1H), 4.68 (brs, 1H), 4.38 (m, 1H), 3.83 (s, 3H), 2.22 (m, 1H), 1.74 (ddd, $J = 14.2$, 6.8, 4.9 Hz, 1H), 1.34 (d, $J = 6.3$ Hz, 3H), 1.29 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 150.39, 146.73, 121.48, 120.53, 116.35, 112.11, 72.07, 68.94, 55.64, 46.07, 42.47, 20.46, 19.71; IR (neat, $cm^{-1}$) 3016, 2111, 1691, 1592, 1502, 1456, 1381, 1253, 756, 667; HRMS (ESI) $m/z$ ($M + Na^+$) calcd for $C_{14}H_{18}N_2NaO_4$ 301.1164, found 301.1245. Data for **1b** (80%): $[\alpha]_D^{20} = +14.8$ (*c* 1.01, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 7.16 (t like, $J = 8.3$ Hz, 1H), 6.53–6.46 (m, 3H), 4.56 (m, 1H), 4.02 (m, 1H), 3.77 (s, 3H), 2.43 (brs, 1H), 1.94 (ddd, $J = 14.6$, 8.8, 8.3 Hz, 1H), 1.66 (ddd, $J = 14.6$, 4.4, 3.4 Hz, 1H), 1.29 (d, $J = 5.9$ Hz, 3H), 1.20 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.78, 158.37, 129.85, 108.25, 106.62, 102.60, 73.64, 66.81, 55.28, 45.55, 23.80, 20.00; IR (neat, $cm^{-1}$) 3400, 2970, 1630, 1590, 1500, 1160, 1050, 770; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1230. Data for **2b** (89%): $[\alpha]_D^{20} = +22.6$ (*c* 1.00, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 7.14 (t, $J = 8.3$ Hz, 1H), 6.47 (dt, $J = 8.3$, 2.4 Hz, 2H), 6.43 (t, $J = 2.4$ Hz, 1H), 5.15 (m, 1H), 4.44 (m, 1H), 3.76 (s, 3H), 3.41 (s, 2H), 2.23 (s, 3H), 2.24 (ddd, $J = 14.2$, 7.8, 6.4 Hz, 1H), 1.70 (ddd, $J = 14.2$, 6.4, 5.4 Hz, 1H), 1.31 (d, $J = 5.9$ Hz, 3H), 1.22 (d, $J = 5.9$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 200.19, 166.40, 160.77, 158.69, 129.77, 107.76, 106.19, 102.14, 70.42, 69.67, 55.22, 50.31, 42.30, 30.10, 20.22, 19.75; IR (neat, $cm^{-1}$) 2979, 1717, 1602, 1492, 1265, 1200, 1150, 766; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1465. Data for **3b** (85%): $[\alpha]_D^{20} = +25.1$ (*c* 1.02, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 7.14 (t, $J = 8.3$ Hz, 1H), 6.46 (dt, $J = 8.3$, 2.0 Hz, 2H), 6.42 (t, $J = 2.0$ Hz, 1H), 5.17 (m, 1H), 4.70 (brs, 1H), 4.41 (m, 1H), 3.76 (s, 3H), 2.14 (ddd, $J = 14.2$, 8.3, 6.3 Hz, 1H), 1.69 (ddd, $J = 14.2$, 6.8, 5.4 Hz, 1H), 1.32 (d, $J = 5.9$ Hz, 3H), 1.27 (d, $J = 5.9$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.65, 158.59, 129.66, 107.50, 106.02, 102.03, 70.42, 68.89, 55.05, 46.08, 42.33, 20.48; IR (neat, $cm^{-1}$) 3019, 2114, 1686, 1601, 1498, 1384, 1216, 1151, 756, 669; HRMS (ESI) $m/z$ ($M + Na^+$) calcd for $C_{14}H_{18}N_2NaO_4$ 301.1164, found 301.1168. Data for **1c** (86%): $[\alpha]_D^{20} = +6.92$ (*c* 1.09, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.87 (d, $J = 9.3$ Hz, 2H), 6.82 (d, $J = 9.3$ Hz, 2H), 4.46 (m, 1H), 4.07 (m, 1H), 3.76 (s, 3H), 2.70 (brs, 1H), 1.89 (m, 1H), 1.68 (ddd, $J = 14.4$, 4.2, 2.9 Hz, 1H), 1.26 (d, $J = 5.9$ Hz, 3H), 1.23 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 154.37, 151.00, 118.06, 114.67, 75.52, 67.21, 55.66, 45.50, 23.70, 19.96; IR (neat, $cm^{-1}$) 3430, 2840, 1510, 1240, 1040, 830; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1242. Data for **2c** (90%): $[\alpha]_D^{20} = +13.7$ (*c* 1.13, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.80 (s, 4H), 5.17 (m, 1H), 4.32 (m, 1H), 3.74 (s, 3H), 3.40 (s, 2H), 2.23 (s, 3H), 2.12 (ddd, $J = 14.2$, 7.8, 6.8 Hz, 1H), 1.68 (dt like, $J = 14.2$, 5.9 Hz, 1H), 1.27 (d, $J = 6.3$ Hz, 3H), 1.25 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 200.26, 166.34, 153.75, 151.31, 117.10, 114.50, 71.44, 69.59, 55.56, 50.25, 42.29, 30.05, 20.17, 19.70; IR (neat, $cm^{-1}$) 2978, 1717, 1507, 1361, 1228, 1036, 958, 829, 735; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1428. Data for **3c** (78%): $[\alpha]_D^{20} = +24.2$ (*c* 1.20, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.80 (s, 4H), 5.18 (m, 1H), 4.70 (brs, 1H), 4.30 (m, 1H), 3.74 (s, 3H), 2.12 (ddd, $J = 14.2$, 8.3, 6.4 Hz, 1H), 1.68 (ddd, $J = 14.2$, 6.4, 4.9 Hz, 1H), 1.28 (d, $J = 6.4$ Hz, 3H), 1.27 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 16.31, 153.91, 151.56, 117.17, 114.64, 71.55, 69.12, 55.68, 46.29, 42.50, 20.62, 19.82; IR (neat, $cm^{-1}$) 3019, 2113, 1684, 1506, 1465, 1382, 1216, 1100, 1038, 827, 759, 668; HRMS (ESI) $m/z$ ($M + Na^+$) calcd for $C_{14}H_{18}N_2NaO_4$ 301.1164, found 301.1181. Data for **1d** (89%): $[\alpha]_D^{20} = +9.85$ (*c* 1.32, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.08 (m, 3H), 4.53 (m, 1H), 4.00 (m, 1H), 3.73 (s, 2H), 2.50 (brs, 1H), 1.91 (ddd, $J = 14.2$, 8.8, 8.3 Hz, 1H), 1.64 (m, 1H), 1.29 (d, $J = 6.8$ Hz, 1H), 1.19 (d, $J = 6.4$ Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.40, 158.98, 94.79, 93.26, 73.45, 66.71, 55.28, 45.49, 23.79, 19.99; IR (neat, $cm^{-1}$) 3420, 2969, 1599, 1476, 1205, 1152, 1067, 820; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{13}H_{20}O_4$, 240.1362, found 240.1338. Data for **2d** (96%): $[\alpha]_D^{20} = +20.3$ (*c* 1.20, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.05 (s, 3H), 5.14 (m, 1H), 4.41 (m, 1H), 3.74 (s, 6H), 3.42 (s, 2H), 2.23 (s, 3H), 2.13 (ddd, $J = 14.2$, 7.8, 6.4 Hz, 1H), 1.69 (m, 1H), 1.30 (d, $J = 6.4$ Hz, 3H), 1.26 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 200.15, 166.28, 161.27, 159.18, 94.27, 92.76, 70.25, 69.39, 55.06, 50.12, 42.08, 29.95, 20.05, 19.59; IR (neat, $cm^{-1}$) 2978, 1717, 1601, 1476, 1200, 1153, 1068, 757, 668; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{17}H_{24}O_6$ 324.1573, found 324.1557. Data for **3d** (91%): $[\alpha]_D^{20} = +8.29$ (*c* 1.17, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.04 (s, 3H), 5.17 (m, 1H), 4.71 (brs, 1H), 4.38 (m, 1H), 3.74 (s, 6H), 2.13 (ddd, $J = 14.2$, 8.3, 6.4 Hz, 1H), 1.68 (ddd, $J = 14.2$, 6.4, 5.4 Hz,), 1.31 (d, $J = 5.9$ Hz, 3H), 1.26 (d, $J = 5.9$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.0, 161.6, 159.5, 95.0, 93.3, 70.9, 69.0, 55.2, 46.0, 42.7, 20.5, 19.9; IR (neat, $cm^{-1}$) 2980, 2115, 1690, 1600, 1475, 1380, 1150, 820; HRMS (ESI) $m/z$ ($M + Na^+$) calcd for $C_{15}H_{20}N_2NaO_5$ 331.1270, found 331.1281. Data for **1e** (94%): $[\alpha]_D^{20} = +10.7$ (*c* 1.00, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.34 (s, 1H), 6.33 (s, 1H), 6.28 (s, 1H), 4.54 (m, 1H), 4.02 (m, 1H), 3.75 (s, 3H), 2.52 (brs, 1H), 2.27 (s, 3H), 1.91 (m, 1H), 1.66 (dt like, $J = 14.4$, 3.4 Hz, 1H), 1.28 (d, $J = 6.2$ Hz, 3H), 1.20 (d, $J = 6.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.69, 158.20, 140.31, 109.32, 107.53, 99.61, 73.77, 67.00, 55.22, 45.51, 23.71, 21.78, 19.99; IR (neat, $cm^{-1}$) 3410, 2971, 2840, 1715, 1470, 1318, 1151, 918, 688;

HRMS (EI) $m/z$ ($M^+$) calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1448. Data for **2e** (93%): $[\alpha]_D^{20} = +16.4$ ($c$ 1.00, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.30 (s, 1H), 6.29 (s, 1H), 6.25 (s, 1H), 5.15 (m, 1H), 4.41 (m, 1H), 3.74 (s, 3H), 3.42 (s, 2H), 2.27 (s, 3H), 2.23 (s, 3H), 2.18 (m, 1H), 1.70 (m, 1H), 1.30 (d, $J = 6.2$ Hz, 3H), 1.26 (d, $J = 6.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 200.62, 166.61, 160.70, 158.60, 140.21, 108.82, 107.06, 99.09, 70.26, 69.74, 55.21, 50.36, 42.28, 30.17, 21.81, 20.18, 19.75; IR (neat, $cm^{-1}$) 2979, 1714, 1594, 1471, 1316, 1150, 957, 830, 689; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{17}H_{24}O_5$ 308.1624, found 308.1672. Data for **3e** (75%): $[\alpha]_D^{20} = +9.8$ ($c$ 0.97, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.30 (s, 1H), 6.28 (s, 1H), 6.24 (s, 1H), 5.17 (m, 1H), 4.71 (s, 1H), 4.40 (m, 1H), 3.74 (s, 3H), 2.27 (s, 3H), 2.13 (ddd, $J = 14.4$, 8.3, 6.2 Hz, 1H), 1.68 (ddd, $J = 14.4$, 6.9, 5.5 Hz, 1H), 1.30 (d, $J = 6.2$ Hz, 3H), 1.26 (d, $J = 6.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.67, 158.61, 146.26, 140.18, 108.70, 107.01, 99.11, 90.35, 70.31, 69.06, 55.19, 42.43, 21.81, 20.57, 19.78; IR (neat, $cm^{-1}$) 3104, 2978, 2359, 2110, 1695, 1594, 1455, 1384, 1151, 936, 830; HRMS (ESI) $m/z$ ($M + Na^+$) calcd for $C_{15}H_{20}N_2NaO_4$ 315.1321, found 315.1285.

**Rhodium Catalyzed Reaction of 3.** The reaction was carried out under the conditions employed for the unsubstituted and other substituted substrates.[4] A typical procedure was as follows: A solution of **3** (100 mg) in dichloromethane (9 mL) was added dropwise to a solution of dirhodium tetraacetate (ca. 5 mg) in dichloromethane (9 mL) in 40–60 min under stirring at rt (22–26 °C). After 30 min, the mixture was concentrated and purified by a silica-gel column (elution with 20–25% ethyl acetate in hexane). Data for **4b** (75%): $[\alpha]_D^{20} = +24.4$ ($c$ 1.61, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 6.17 (ddd, $J = 9.4$, 6.8, 1.1 Hz, 1H), 5.85 (dd, $J = 9.4$, 5.5 Hz, 1H), 5.78 (s, 1H), 5.76 (d, $J = 6.8$ Hz, 1H), 4.87 (m, 1H), 4.35 (m, 1H), 3.66 (s, 3H), 3.12 (d, $J = 5.5$ Hz, 1H), 1.99 (ddd, $J = 15.1$, 11.2, 9.3 Hz, 1H), 1.81 (dd, $J = 15.1$, 3.9 Hz, 1H), 1.34 (d, $J = 5.9$ Hz, 3H), 1.28 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 169.57, 156.97, 152.23, 124.35, 116.58, 109.41, 102.74, 84.52, 73.39, 54.83, 47.53, 45.66, 22.64, 22.24; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1254. Data for **4c** (70%): $[\alpha]_D^{20} = -119.5$ ($c$ 0.48, $CH_3OH$); $^1$H NMR ($CDCl_3$) $\delta$ 6.19 (dd, $J = 10.3$, 5.9 Hz, 1H), 6.09 (d, $J = 10.3$ Hz, 1H), 5.86 (d, $J = 7.3$ Hz, 1H), 5.59 (d, $J = 7.3$ Hz, 1H), 4.83 (m, 1H), 4.25 (m, 1H), 3.64 (s, 3H), 3.12 (d, $J = 5.9$ Hz, 1H), 1.98 (ddd, $J = 15.1$, 11.2, 8.8 Hz 1H), 1.83 (dd like, $J = 15.1$, 4.4 Hz, 1H), 1.34 (d, $J = 6.3$ Hz, 3H), 1.32 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 169.52, 158.56, 145.99, 123.21, 122.72, 110.28, 100.42, 84.45, 73.35, 54.92, 47.21, 45.41, 22.78, 22.33; IR (neat, $cm^{-1}$) 2975, 2360, 1731, 1634, 1580, 1507, 1378, 1082, 1017, 925, 731; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1178. Data for **4d** (not isolated): $^1$H NMR ($CDCl_3$) $\delta$ 5.64 (s, 1H), 5.60 (s, 1H), 5.08 (d, $J = 5.2$ Hz, 1H), 4.82 (dqd, $J = 15.2$, 6.2, 2.7 Hz, 1H), 4.30 (dqd, $J = 15.2$, 6.2, 4.1 Hz, 1H), 3.65 (s, 3H), 3.59 (s, 3H), 3.39 (d, $J = 5.2$ Hz, 1H), 1.80 (dd, $J = 15.2$, 4.1 Hz, 1H), 1.34 (d, $J = 6.2$ Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.98, 155.12, 108.42, 99.89, 99.63, 85.01, 73.38, 65.85, 55.95, 54.82, 45.29, 45.04, 22.69, 22.12, 15.27. Data for **4e** (not isolated): $^1$H NMR ($CDCl_3$) $\delta$ 568 (s, 1H), 5.65 (s, 1H), 5.64 (d, $J = 5.3$ Hz, 1H), 4.79 (dqd, $J = 15.2$, 6.3, 2.4 Hz, 1H), 4.26 (dqd, $J = 15.2$, 6.3, 3.9 Hz, 1H), 3.56 (s, 3H), 3.28 (d, $J = 5.3$ Hz, 1H), 1.98 (m, 1H), 1.89 (s, 3H), 1.82 (d, $J = 15.2$, 3.9 Hz, 1H), 1.34 (d, $J = 6.3$ Hz, 3H), 1.33 (d, $J = 6.3$ Hz, 3H).

**Brønsted Acid Promoted Rearrangement of 4 to Give 5.** A solution of **4b** (69 mg) in ether (5 mL) was stirred in the presence of $p$-toluenesulfonic acid (ca. 3 mg) in 6 h at rt. The mixture was extracted and purified by column chromatography on silica gel (elution with 30% ethyl acetate in hexane) to give **5b** (40 mg, 57%). Isolation of **5d** obtained by the reaction of **3d** was accomplished by a silica-gel column (30% ethyl acetate in hexane) in 76.2% yield. A mixture of **4e** and **4e′** (3:1) was converted to a mixture of **5e** and **5e′** by passing repeatedly a short silica-gel column (elution with 30% ethyl acetate in hexane). The conversion was quantitative, but the produced **5e** and **5e′** were not separable. The $^1$H NMR signals for this mixture were assigned to the respective isomers by the COSY experiment. Substrate **6** employed for the acid isomerization was prepared by the reaction of anisole with ethyl diazoacetate, and isolated by a silica-gel column (6% ethyl acetate in hexane). Produced **7** was identified by comparing with the reported spectral data.[8] Data for **5b**: $[\alpha]_D^{20} = +120.5$ ($c$ 1.23, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 6.50 (d, $J = 9.3$ Hz, 1H), 5.27 (ddd, $J = 9.3$, 8.3, 5.9 Hz, 1H), 5.16 (d, $J = 1.5$ Hz, 1H), 4.70 (m, 1H), 3.89 (m, 1H), 3.64 (s, 3H), 3.05 (ddd, $J = 13.7$, 8.3, 1.5 Hz, 1H), 2.10 (dd, $J = 13.7$, 5.9 Hz, 1H), 1.98 (ddd, $J = 15.1$, 11.7, 9.8 Hz, 1H), 1.72 (dd, $J = 15.1$, 3.4 Hz, 1H), 1.27 (d, $J = 6.4$ Hz, 3H), 1.26 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.47, 159.80, 158.95, 126.23, 117.02, 115.7, 95.41, 77.31, 74.09, 56.56, 44.76, 33.40, 23.03, 22.37; IR (neat, $cm^{-1}$) 1700, 1610, 1540, 1255, 1130, 1085, 670; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1220. Data for **5d**: $[\alpha]_D^{20} = +58.7$ ($c$ 1.02, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.31 (d, $J = 1.5$ Hz, 1H), 5.16 (s, 1H), 4.45 (dqd, $J = 10.3$, 6.4, 1.0 Hz, 1H), 3.84 (dqd, $J = 11.2$, 6.4, 2.9 Hz, 1H), 3.68 (s, 3H), 3.58 (s, 3H), 2.90 (dd, $J = 14.2$, 1.5 Hz, 1H), 2.65 (d, $J = 14.2$ Hz, 1H), 1.88 (ddd, $J = 15.1$, 11.2, 10.3 Hz, 1H), 1.64 (ddd, $J = 15.1$, 2.9, 1.0 Hz, 1H), 1.25 (d, $J = 6.4$ Hz, 3H), 1.24 (d, $J = 6.4$ Hz, 3H); IR (neat, $cm^{-1}$) 1680, 1630, 1530, 1345, 1255, 1155, 1080; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1325. Data for **5e**: $^1$H NMR ($CDCl_3$) $\delta$ 5.92 (s, 0.7H), 5.21 (s, 0.7H), 4.41 (m, 0.7H), 3.75 (m, 0.7H), 3.61 (s, 2.1H), 2.93 (dd, $J = 14.1$, 1.7 Hz, 0.7H), 2.52 (d, $J = 14.1$ Hz, 0.7H), 2.10 (d, $J = 1.0$ Hz, 2.1H), 1.26 (d, $J = 6.5$ Hz, 4.2 H). Data for **5e′**: $^1$H NMR ($CDCl_3$) $\delta$ 5.82 (s, 0.3H), 5.46 (d, $J = 1.7$ Hz, 0.3H), 4.41 (m, 0.3H), 3.81 (m, 0.3H), 3.68 (s, 0.9H), 2.72 (dd, $J = 13.7$, 0.7 Hz, 0.3H), 2.42 (d, $J = 13.7$ Hz, 0.3H), 1.98 (d, $J = 1.0$ Hz, 0.9H), 1.27 (d, $J = 6.5$ Hz, 0.9H); $^{13}$C NMR for a mixture of **5e** and **5e′** ($CDCl_3$) $\delta$ 169.77, 169.20, 165.82, 159.84, 159.74, 157.18, 147.71, 143.32, 119.42, 118.34, 101.43, 100.19, 99.95, 98.89, 76.64, 74.79, 74.67, 55.99, 54.99, 53.41, 44.27, 44.22, 31.69, 30.75, 26.28, 24.45, 23.16, 23.11, 22.38, 22.32.

**Lewis Acid Promoted Reaction of 4 to Give 10.** The reaction was carried out by the addition of zinc iodide (ca. 5 mg) to a solution of **4b** (15–20 mg) in ether at rt (12 h). The same reaction of **4b** was also carried out with tin(IV) chloride (ca. 0.02 mL) in dichloromethane at rt (30 min), or boron trifluoride etherate (ca. 0.02 mL) in ether at 0 °C (30 min). Extraction and concentration gave essentially pure **10b** in all cases. The treatment of **4e** (7.5 mg) with diethyl ether–boron trifluoride (1/1, 0.01 mL) in ether (45 min), followed by extraction and purification with a short silica-gel column (elution with 60% ethyl acetate in hexane), gave **10e** (7.2 mg). Data for **10b**: $[\alpha]_D^{20} = +100.3$ ($c$ 1.40, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 6.99 (d, $J = 8.3$ Hz, 1H), 6.58 (d, $J = 2.4$ Hz, 1H), 6.52 (dd, $J = 8.3$, 2.4 Hz, 1H), 4.53 (brs, 1H), 4.12 (m, 1H), 3.76 (s, 3H), 3.54 (d, $J = 16.1$ Hz, 1H), 3.40 (d, $J = 16.1$ Hz, 1H), 1.98 (ddd, $J = 15.1$, 11.2, 10.2 Hz, 1H), 1.51 (d, $J = 6.3$ Hz, 3H), 1.50 (d, $J = 6.8$ Hz, 3H), 1.48 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.48, 159.54, 159.18, 130.23, 121.20,

107.38, 106.44, 81.86, 74.91, 55.40, 40.20, 39.21, 24.21, 21.13; IR (neat, $cm^{-1}$) 2972, 2932, 2837, 1733, 1612, 1582, 1506, 1445, 1328, 1296, 1260, 1227, 1196, 1158, 1124, 1092, 978, 918, 853; HRMS (EI) $m/z$ ($M^+$) calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1250. Data for **10e**: $[\alpha]_D^{20} = +23$ ($c$ 0.3, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) $\delta$ 6.44 (d, $J = 2.4$ Hz, 1H), 6.42 (d, $J = 2.4$ Hz, 1H), 4.9 (dm, 1H), 4.14 (m, 1H), 3.75 (s, 3H), 3.51 (d, $J = 16.5$ Hz, 1H), 3.27 (d, $J = 16.5$ Hz, 1H), 2.56 (m, 1H), 2.22 (s, 3H), 1.54 (d, $J = 6.9$ Hz, 3H), 1.51 (d, $J = 6.6$ Hz, 3H), 1.50 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 174.68, 159.46, 158.77, 137.51, 119.46, 109.31, 103.04, 65.87, 55.28, 39.07, 35.49, 24.17, 21.17, 20.54, 15.25; IR (neat, $cm^{-1}$) 2921, 1733, 1606, 1487, 1445, 1376, 1310, 1244, 1195, 1092, 920; HRMS (ESI) $m/z$ ($M + Na^+$) calcd for $C_{15}H_{20}NaO_4$ 287.1259, found 287.1339.

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