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Enantiocontrolled Synthesis of Jasmonates via Tandem Retro-Diels–Alder–Ene Reaction Activated by a Silyl Substituent

Katsufumi Suzuki, Kohei Inomata,* and Yasuyuki Endo

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981−8558, Japan

inomata@tohoku-pharm.ac.jp

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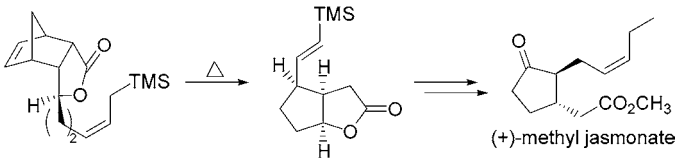
ABSTRACT



An enantiocontrolled synthesis of (−)-methyl 6-*epi*-cucurbate and (+)-methyl jasmonate was established from a chiral tricyclic lactone via a new type of tandem retro-Diels–Alder–ene reaction activated by a trimethysilyl substituent as the key step.

Recently, we reported a new chiral synthesis of optically pure γ-mono- or γ-disubstituted butenolides from a tricyclic lactone (−)-**1** via a thermal retro-Diels−Alder reaction.[1] We report here a new application of our procedure to prepare 5,5-fused bicyclic lactone **5** by employing a tandem retro-Diels−Alder−ene (RDAE) reaction[2,3] activated by a trimethylsilyl (TMS) substituent as the key step, allowing us to establish an enantiocontrolled synthesis of methyl 6-*epi*-cucurbate (see ref 20) **11**[4] and methyl jasmonate **13**,[5] which are plant growth regulators,[6,7] in the unnatural forms.

In the present study, we synthesized tricyclic lactones **3a** and **3b** (see ref 21) with a (*Z*)- and (*E*)-homocrotyl moiety from (−)-**1**[8] by the application of our established method.[1] Thus, optically pure (−)-**1** was allowed to react with diisobutylaluminum hydride (DIBAL) and then to react continuously with Grignard reagent, prepared from (*Z*)-[9] or (*E*)-5-bromopent-2-ene,[10] in the same flask to yield the diols **2a**, $[\alpha]^{20}_{D}$ −56.9 (*c* 1.00, $CHCl_3$), and **2b**, $[\alpha]^{18}_{D}$ −64.3 (*c* 1.20, $CHCl_3$), respectively, each as a single material. The diols **2a** and **2b** were oxidized to lactones **3a**, $[\alpha]^{22}_{D}$ +16.7 (*c* 1.00, $CHCl_3$), and **3b**, $[\alpha]^{17}_{D}$ +21.9 (*c* 1.00, $CHCl_3$), by using a catalytic amount of tetrapropylammonium perruthenate (TPAP) with 4-methyl morpholine-4-oxide (NMO) in

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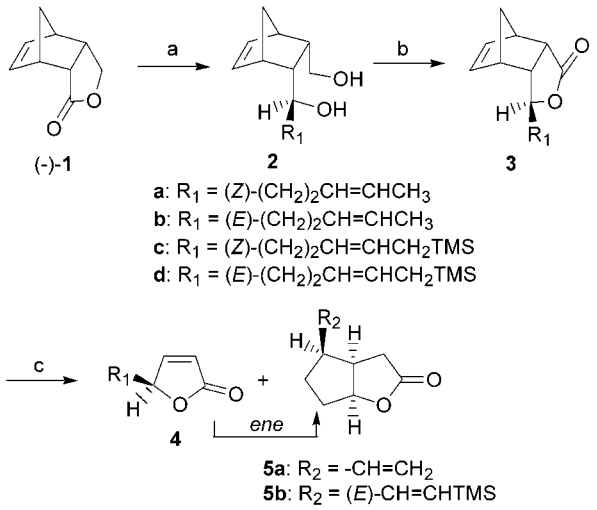
moderate yield.[11] The results of RDAE reaction of **3a** and **3b** in refluxing diphenyl ether (Ph_2O) are summarized in Table 1. In the case of using **3a**, the RDAE reaction proceeded to afford an inseparable mixture of the butenolide **4a** as a product of retro-Diels−Alder reaction and the known all-*cis* fused bicyclic lactone **5a**[12] as a product of ene reaction, which would have occurred after retro-Diels−Alder reaction, after 2 h (entry 1). Prolonging the reaction time increased the formation ratio of **5a** but decreased the total yield (entry 2). RDAE reaction of **3b** also proceeded to yield an inseparable mixture of butenolide **4b** and bicyclic lactone **5a** with a lower formation ratio of **5a** than in the case of using **3a**, even after 18 h (entry 3). To overcome the lower reactivity and lower yield of the ene reaction, we next examined the use of a silyl substituent, which was expected to show strong hyperconjugation to the π-orbital of the alkene moiety and to provide a higher energy level of highest occupied molecular orbital (HOMO) for the ene reaction. Thus, the diols **2c**, $[\alpha]^{18}_D$ −46.6° (*c* 1.10, $CHCl_3$), and **2d**, $[\alpha]_D^{20}$ −54.6 (*c* 0.82, $CHCl_3$), bearing a trimethylsilyl (TMS) substituent, were prepared from (−)-**1** by nucleophilic addition similar to that described above, with DIBAL and Grignard reagent prepared from (*Z*)-[13] and (*E*)-5-bromo-1-(trimethylsilyl)pent-2-ene.[14] After oxidation of **2c** and **2d**, RDAE reactions of lactones **3c**, $[\alpha]^{16}_D$ +6.6° (*c* 1.00, $CHCl_3$), and **3d**, $[\alpha]_D^{20}$ +6.2 (*c* 1.12, $CHCl_3$), were conducted (Table 1, entries 4−6). The RDAE reaction of **3c** proceeded smoothly to yield a single bicyclic lactone **5b**[15] in 75% yield together with a very small amount of butenolide **4c**, which was readily separated by silica gel column chromatography. On the other hand, in the case of using **3d**, the RDAE reaction afforded a separable mixture of butenolide **4d** and the same lactone **5b**, which was obtained from **3c**, in 70% yield with a 51:49 formation ratio after 3 h (entry 5), and in 30% yield with an 8:92 ratio after 18 h (entry 6). (*E*)-Configuration of the generated vinyl silane in **5b** was indicated by the *J*-values of the alkenic protons (δ 5.73, dd, J = 18.8, 1.5 Hz; δ 5.97, dd, J = 18.8, 5.4 Hz) of **5b** in the ^{1}H NMR spectra. This result suggested that RDAE reaction of **3c** and **3d** proceeded stereoselectively to construct the (*E*)-vinyl silane (Scheme 1).

Table 1. RDAE Reaction of Lactone **3**

entry	substrate	time (h)	yield[a] (%)	ratio[b] (**4**:**5**)
1	**3a**	2	74	33:67
2	**3a**	18	38	6:94
3	**3b**	18	43	56:44
4	**3c**	3	75	>1:99
5	**3d**	3	70	51:49
6	**3d**	18	30	8:92

[a] Combined yield. [b] Ratios of **4**:**5** were determined from the ^{1}H NMR spectra at 270 MHz of the crude products by integration of the signals due to the β-proton of the butenolide **4** and the olefinic methine or methylene proton of the bicyclic lactone **5**.

Scheme 1[a]



[a] Reagents and conditions: (a) DIBAL (1.1 equiv), THF, −78 °C, 40 min to 1 h, then R_1MgBr (4.0 equiv), −78 °C, 15−18 h; **2a**, 79%; **2b**, 85%; **2c**, 79%; **2d**, 62%. (b) TPAP (5 mol%), NMO (3.0 equiv), 4 Å molecular sieves (0.7 g/1 mmol of a substrate), CH_2Cl_2, 0 °C to rt, 4−48 h; **3a**, 56%; **3b**, 67%; **3c**, 68%; **3d**, 58%. (c) Ph_2O, reflux; see Table 1.

In all cases of the RDAE reaction, the starting lactone **3** was no longer detectable in the reaction mixture after 2 h, and only **5** was obtained as a corresponding ene product without other stereoisomeric bicyclic lactones, despite the geometry of the alkene moiety in **3**. These results suggested that the rate-determining step of the RDAE reaction was the ene process and that the ene reaction proceeded through the *exo* transition state **6a** in the cases of butenolides **4a** and **4c**

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(14) (*E*)-5-Bromo-1-(trimethylsilyl)pent-2-ene was prepared from (*E*)-5-(tetrahydropyran-2-yloxy)pent-2-en-1-ol[18] by using the following method: (i) bromination of alcohol [triphenylphosphine (Ph_3P), CBr_4]; (ii) substituition with trimethylsilyllithium[19] [$(TMS)_2$, methyllithium]; (iii) deprotection of tetrahydropyranyl (THP) ether (*p*-toluenesulfonic acid, CH_3OH); and (iv) bromination of the generated alcohol (Ph_3P, CBr_4).

(15) Data for **5b**. Mp: 53−54 °C. $[\alpha]^{20}_D$ +27.6 (*c* 0.98, $CHCl_3$). IR (film): ν 1756 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) 0.07 (9H, s, −Si(C*H*$_3$)$_3$), 1.51−1.64 (1H, m, −CH=CHCHC*H*$_2$−), 1.66−1.85 (2H, m, −OCHC*H*$_2$−, CH=CHCHC*H*$_2$−), 2.09 (1H, dd, J = 13.0 Hz, 6.8 Hz, −OCHC*H*$_2$−), 2.39 (1H, dd, J = 18.9 Hz, 5.1 Hz, −COC*H*$_2$−), 2.51 (1H, dd, J = 18.9 Hz, 10.4 Hz, −COC*H*$_2$−), 2.62−2.74 (1H, m, −SiCH=CHC*H*−), 2.97−3.09 (1H, m, −COCH$_2$C*H*−), 5.03−5.08 (1H, m, −COOC*H*−), 5.73 (1H, dd, J = 18.8 Hz, 1.5 Hz, −CH=C*H*Si−), 5.97 (1H, dd, J = 18.8 Hz, 5.4 Hz, −C*H*=CHSi−). ^{13}C NMR (67.5 MHz, $CDCl_3$) −1.2 [−Si(*C*H$_3$)$_3$], 26.9 (−CH=CHCHCH$_2$−), 29.8 (−COCH$_2$−), 32.9 (−OCHCH$_2$−), 41.0 (−COCH$_2$*C*H−), 48.5 (−CH=C*H*CH−), 85.9 (−O*C*HCH$_2$−), 133.0 (−CH=*C*HSi−), 144.4 (−*C*H=CHSi−), 177.8 (−*C*O−). EIMS: *m*/*z* 224 (M^+), 209 (100%). HRMS: calcd for $C_{12}H_{20}O_2Si$, 224.1233; found, 224.1222.

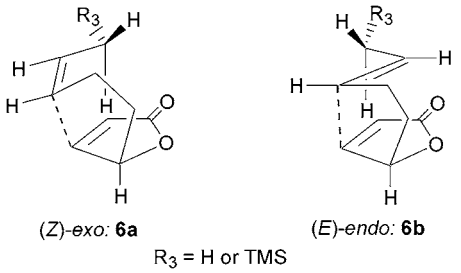
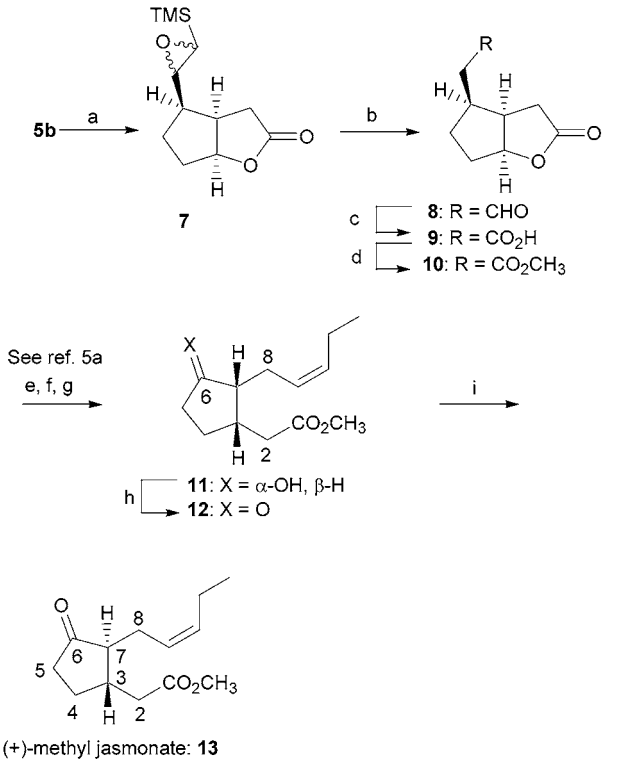


Figure 1. Transition states of the butenolide **4** in the ene reaction.

bearing (*Z*)-alkene and through the *endo* transition state **6b** in the cases of butenolides **4b** and **4d** bearing (*E*)-alkene to yield the bicyclic lactone **5** as a single product of the ene reaction (Figure 1). The lower formation ratios of **5** in entries 3 and 5 suggested that the ene reactions of **4b** and **4d** were very slow and that **6b** was a disfavored transition state compared with **6a** because of its highly strained framework. A comparison of the pairs of entries 2,4 and 3,6 shows that the TMS substituent clearly activated the ene process of the RDAE reaction. From these results, we concluded that the substrate **3c** bearing the (*Z*)-alkene with the TMS substituent was most suitable for the RDAE reaction to construct a 5,5-fused bicyclic lactone such as **5b**.

We next utilized the above result to establish a synthesis of (−)-methyl 6-*epi*-cucurbate **11** and (+)-methyl jasmonate **13** from **5b**. In practice, the lactone **5b** was converted to a diastereomeric mixture of epoxide **7** (dr = 2:1) by using *m*-chloroperbenzoic acid (*m*CPBA). Without further purification or stereostructure determination of **7**, acidic treatment of **7** with perchloric acid afforded the aldehyde **8** *via* epoxide ring opening and desilylation.[16] After oxidation of **8** to the carboxylic acid **9** by using Jones' reagent, esterification of **9** with diazomethane afforded the known ester **10**, $[\alpha]^{18}_D$ +21.7 (*c* 1.6, $CHCl_3$), {lit.[5a] $[\alpha]^{20}_D$ +22.5 (*c* 0.63, $CHCl_3$)}, which was the key intermediate for the synthesis of **11** and **13** previously reported by Montforts et al.[5a] These chemical correlations from **5b** to **10** suggested that the expected stereochemistry of the chiral centers in **5b**, newly generated by the RDAE reaction, was correct. According to the established method,[5a] the ester **10** was transformed to **11**, $[\alpha]^{20}_D$ −9.5 (*c* 0.80, CH_3OH), {lit.[4d] antipode: $[\alpha]^{24}_D$ +10.7 (*c* 0.48, CH_3OH)}. After Dess−Martin periodinate[17] oxidation of **11** to the ketone **12**, clean and complete isomerization occurred upon known basic treatment[5a] (Scheme 2) to afford the single product **13**, $[\alpha]^{20}_D$ +88.7° (*c* 0.7, CH_3OH), {lit.[5a] $[\alpha]^{20}_D$ +90.4 (*c* 0.31,CH_3OH)}.

Scheme 2[a]



[a] Reagents and conditions: (a) *m*CPBA (2.5 equiv), CH_2Cl_2, 0 °C to rt, 15 h, 88%; (b) 70% $HClO_4$ (20 equiv), THF/H_2O (1:1), 0 °C, 3 h; (c) Jones reagent (3.0 equiv), acetone, 0 °C, 50 min; (d) CH_2N_2 (30 equiv), Et_2O, rt, 0.5 h, 60% from **7**; (e) DIBAL (1.1 equiv), THF, −78 °C, 45 min; (f) $Ph_3P^+C_3H_7Br^-$ (4.0 equiv), NaHMDS (5.0 equiv), −78 °C to rt, 0.5 h; (g) KOH (10 equiv), CH_3OH, rt, 6 h, then CH_2N_2 (2.0 equiv), CH_2Cl_2, rt, 0.5 h, 37% from **10**; (h) Dess−Martin periodinate (1.1 equiv), CH_2Cl_2, rt, 0.5 h, 94%; (i) triethylamine (solvent), sealed tube, 135 °C, 3 h, 100%.

In conclusion, we have established an enantiocontrolled synthesis of (−)-methyl 6-*epi*-cucurbate **11** and (+)-methyl jasmonate **13** *via* a new type of tandem RDAE reaction activated by a silyl substituent. The natural antipodes (+)-**11** and (−)-**13** would be obtainable by the same method from the enantiomeric lactone (+)-**1**, which has already been prepared.[8] We have also found that a TMS substituent strongly activated an alkene with low reactivity in the ene reaction and that the tandem RDAE reaction of **3c** proceeded stereoselectively to yield bicyclic lactone **5b** bearing (*E*)-vinyl silane. We have just begun to investigate exploitation of **5b** as a new chiral synthon to synthesize pharmaceutically more important compounds such as prostanoids. We have also begun to study the scope and limitations of the tandem RDAE reaction activated by silyl substituents.

Supporting Information Available: Experimental procedures and data and spectra for various compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The numbering for a fatty acid was used.
(21) All new compounds gave the expected analytical (combustion and/or high-resolution mass) and spectral (IR, NMR, and mass) data.