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NEW CHIRAL SYNTHESIS OF METHYL AND ALLYL DISUBSTITUTED BUTYRO LACTONE: A FORMAL SYNTHESIS OF (–)-NGAIONE

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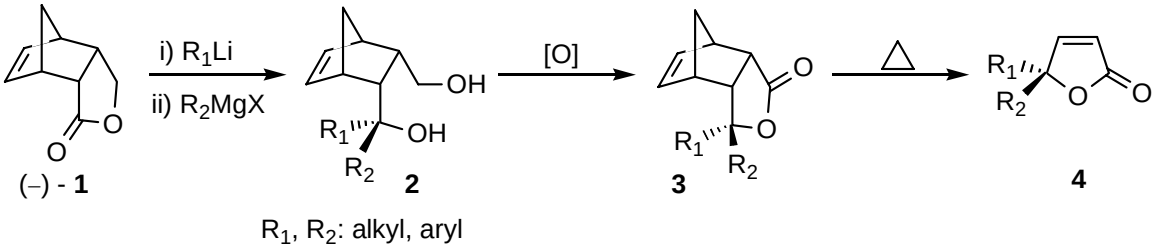
Abstract – A new chiral synthesis of butyrolactone [(–)-**7**] bearing methyl and allyl substituents at the γ-position has been established *via* diastereoselective continuous nucleophilic addition to the chiral tricyclic lactone [(–)-**1**] as the key step. In practice, continuous nucleophilic addition to the tricyclic lactone [(–)-**1**] by using the combination of methyllithium and allylmagnesium bromide proceeded to yield the corresponding diol (**8**) diastereoselectively. After oxidation of **8**, enantiopure methyl and allyl disubstituted butenolide (**10**) was obtained *via* retro-Diels-Alder reaction. Selective 1,4-reduction of **10** afforded the corresponding butyrolactone [(–)-**7**], which is the key intermediate for (–)-ngaione synthesis.

Chiral γ–substituted butenolides (**4**) are known to be useful synthons for the enantiocontrolled construction of a variety of biologically active natural and unnatural compounds.[1] Therefore, chiral synthesis of γ-substituted butenolides has been an ongoing challenge for researchers attempting the organic synthesis of certain substances.[2,3] We have recently reported enantiocontrolled syntheses of versatile chiral γ–substituted butenolides (**4**), bearing various alkyl and aryl substituents at the γ-position, *via* continuous nucleophilic addition to the tricyclic lactone [(–)-**1**] as the key step.[4] In that report, nucleophilic addition to (–)-**1** by using the combination of alkyl- or aryllithium (R_1Li) and alkylmagnesium halide (R_2MgX) proceeded to yield the diol (**2**) and to construct the chiral tertiary hydroxyl group diastereoselectively. After oxidation of **2** to the corresponding lactone (**3**), a thermal retro-Diels-Alder reaction of **3** gave the butenolide (**4**) in high yield (Scheme 1). We report here a new application of this methodology to synthesize chiral γ–methyl and γ-allyl disubstituted butyrolactone [(–)-**7**] and to establish a formal synthesis of (–)-ngaione [(–)-**5**].

(–)–Ngaione [(–)–**5**] was first isolated from the essential oil of *Myporum laetum* (the New Zealand 'ngaio' tree) in 1925[5] and was also identified as a toxic constituent of the stock-poisoning shrub (*Myporum deserti*).[6] The absolute configuration of (–)–**5** was confirmed as 1*S*, 4*R* by Sutherland and

co-workers.[6,7] The antipode of (–)–**5** is known as (+)-ipomeamarone [(+)-**5**], which was isolated from mold-damaged sweet potato (*Ipomea batatas*), and shown to be a phytoalexin.[8] Kubota elucidated the relative structure of (+)-**5**,[9] and the absolute configuration was revised to 1*R*, 4*S* by Nakanishi and co-workers (Figure 1).[10]



Scheme 1

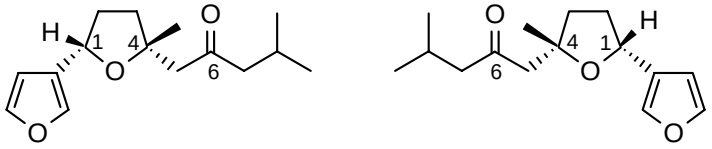
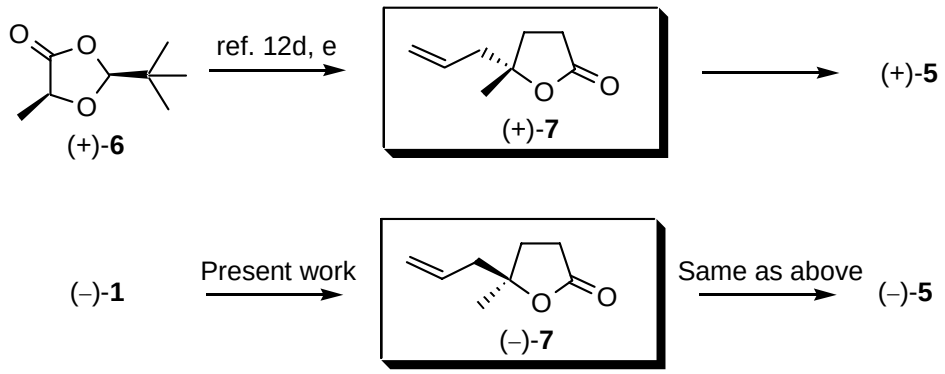


Figure 1

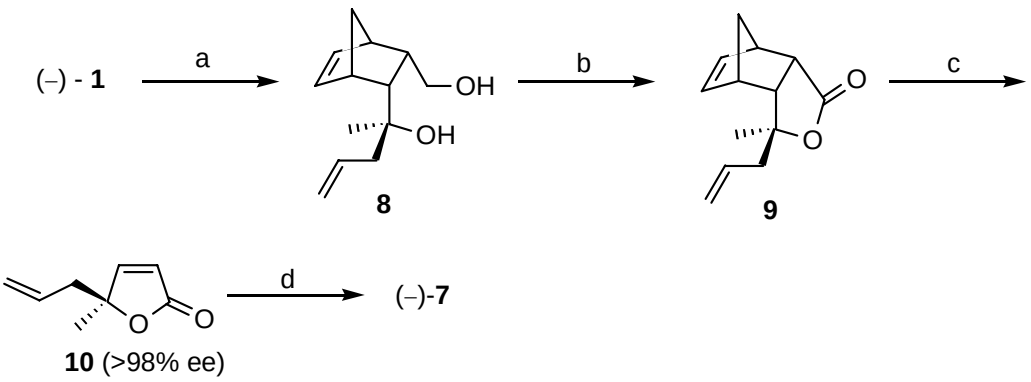
To date, several racemic and chiral syntheses of (+)- and (–)-**5** have been reported.[11,12] In view of the latent chiral tertiary hydroxyl moiety at C-4 in the central tetrahydrofuran ring of **5**, efficient construction of the chiral tertiary hydroxyl group was expected to be important for the total synthesis of **5**. Indeed, Matsuo and co-workers reported an enantiocontrolled total synthesis of (+)-ipomeamarone [(+)-**5**] *via* the chiral butyrolactone [(+)-**7**], which included a chiral tertiary hydroxyl moiety and was prepared from the chiral dioxolanone [(+)-**6**], as a key intermediate.[12d,e] That report suggested that (–)-ngaione [(–)-**5**] might be synthesized from the enantiomeric lactone [(–)-**7**] by using the same methodology. We report here the preparation of (–)-**7** from (–)-**1** by the application of our butenolide synthesis (Scheme 2).

In the present study, optically pure tricyclic lactone [(–)-**1**], prepared from dicyclopentadiene by our established method,[13] was allowed to react with a stoichiometric amount of methyllithium, and then to react continuously with allylmagnesium bromide in the same flask to furnish the diol (**8**) diastereoselectively as a single product in 81% yield. The observed high diastereoselectivity in this reaction was consistent with the result previously reported by us.[4] Oxidation of the diol (**8**) with a catalytic amount of tetrapropylammonium perruthenate (TPAP)[14] in the presence of 4-methylmorpholine *N*-oxide (NMO) gave the corresponding lactone (**9**), in 78% yield. A retro-Diels-Alder reaction of **9** in refluxing diphenyl ether[15] (Ph_2O) afforded a corresponding γ-substituted butenolide (**10**) in 76% yield. Optical purity of **10** was determined to be >98% ee by HPLC with a chiral stationary phase.

Chemoselective reduction of the α,β-unsaturated lactone with the combination of DIBALH and copper(I) iodide in THF-HMPA proceeded very cleanly to yield the desired butyrolatone [(–)-**7**] in 81% yield.[16] The optical rotation value and spectral data of (–)-**7** were identical with those of (+)-**7** (Scheme 3).[12e]



Scheme 2



Scheme 3. *Reagents and conditions*: a. methyllithium, toluene, –78°C, 2 h, then allylmagnesium bromide, –30 °C ~ rt, 10 h; b. TPAP, NMO, 4Å molecular sieves, CH_2Cl_2, 0 °C~rt, 4 h; c. Ph_2O, reflux, 2 h; d. DIBALH, CuI, THF-HMPA (4:1), –78 °C, 0.5 h.

In conclusion, we established a new chiral synthesis of the butyrolactone [(–)-**7**], which is the key intermediate in the total synthesis of (–)-ngaione [(–)-**5**], from tricyclic lactone [(–)-**1**] in 4 steps. The antipode [(+)-**7**] is expected to be synthesized similarly from the enantiomeric lactone [(+)-**1**], which has already been prepared.[13] We are also developing a new type of total synthesis of (+)- and (–)-**5** on the basis of this work.

EXPERIMENTAL

IR spectra were recorded on a JASCO FT–IR–5000 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL-EX-270 (^{1}H: 270 MHz, ^{13}C: 67.5 MHz) spectrometer. MS spectra were recorded on a JEOL-DX-303 spectrometer. Optical purity was determined using a Waters HPLC 600 instrument

equipped with a chiral stationary phase. Optical rotations were measured with a JASCO DIP–370 digital polarimeter.

(1*S*)-1-[(2'*R*, 3'*S*)-3-Hydroxymethylbicyclo[2.2.1]hept-5-en-2-yl]-1-methylbut-3-en-1-ol (8)

To a stirred solution of lactone [(–)-**1**] (400 mg, 2.70 mmol) in anhydrous toluene (8.0 mL) was added methyllithium (2.8 mL, 1.0 M in ether, 2.90 mmol) at –78°C. The mixture was stirred for 2 h, then allylmagnesium bromide (8.0 mL, 1.0 M in ether, 8.0 mmol) was added. The mixture was further stirred for 10 h at –30°C to rt. Sat. aq. NH_4Cl was added to the mixture to quench the reaction. The whole mixture was extracted with ethyl acetate (AcOEt). The combined AcOEt layer was washed with sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. The AcOEt layer was evaporated under reduced pressure and the residue was chromatographed (silica gel: 17 g, eluent: AcOEt/hexane = 1:3) to give the diol (**8**) (457 mg, 81%) as a colorless oil.

8: $[\alpha]_D^{20}$ –6.3° (*c* 1.00, $CHCl_3$). IR (film) : ν 3240 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.15 (3H, s), 1.36 (1H, d, *J* = 8.1 Hz), 1.42 (1H, td, *J* = 8.1 Hz, 1.9 Hz), 2.32-2.38 (2H, m), 2.43 (1H, dd, *J* = 9.7 Hz, 2.9 Hz), 2.63-2.67 (1H, m), 2.85 (2H, br s), 2.95 (2H, br s, D_2O exchangeable), 3.71-3.74 (2H, m), 5.13-5.20 (2H, m), 5.89-5.96 (1H, m), 6.15-6.19 (2H, m). ^{13}C NMR ($CDCl_3$) δ 26.7, 46.1, 47.1, 47.3, 48.6, 50.6, 50.9, 52.5, 64.0, 119.1, 133.7. 134.9, 135.3. EIMS: *m*/*z* 208 (M^+), 66 (100 %). HRMS: calcd for $C_{13}H_{20}O_2$ 208.1463. Found 208.1474.

(1*R*, 2*S*, 5*S*, 6*R*, 7*S*)-5-Allyl-5-methyl-4-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one (9)

To a stirred suspension of the diol (**8**) (450 mg, 2.20 mmol) and 4Å molecular sieves (1.5 g, crushed and dried, 0.7 g / 1 mmol of substrate) in anhydrous CH_2Cl_2 (20 mL) was added NMO (760 mg, 6.50 mmol) and TPAP (38 mg, 0.10 mmol) at 0°C. Stirring was continued for 4 h at rt, then the mixture was filtered through a Celite pad and the filtrate was extracted with CH_2Cl_2. The combined organic layer was washed with sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. The mixture was evaporated under reduced pressure and the residue was chromatographed (silica gel: 12 g, eluent: AcOEt/hexane = 1:5) to give the lactone (**9**) (350 mg, 78%) as a colorless oil.

9: $[\alpha]_D^{24}$ +76.5° (*c* 1.90, $CHCl_3$). IR (film): ν 1758 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.34 (3H, s), 1.42 (1H, dt, *J* = 8.4 Hz, 1.5 Hz), 1.62 (1H, dt, *J* = 8.4 Hz, 1.8 Hz), 2.34 (2H, dd, *J* = 7.3 Hz, 1.0 Hz), 2.78 (1H, dd, *J* = 8.8 Hz, 3.8 Hz), 3.00-3.03 (1H, m), 3.23-3.27 (1H, m), 3.38 (1H, dd, *J* = 8.9 Hz, 5.1 Hz), 5.10-5.18 (1H, m), 5.19-5.22 (1H, m), 5.70-5.86 (1H, m), 6.22-6.28 (2H, m). ^{13}C NMR ($CDCl_3$) δ 22.4, 45.2, 45.5, 49.2, 49.6, 49.7, 52.9, 85.6, 120.3, 134.9, 131.9, 136.1, 177.5. EIMS: *m*/*z* 204 (M^+), 97 (100 %). HRMS: calcd for $C_{13}H_{16}O_2$ 204.1150. Found 204.1181.

(5*S*)-5-Allyl-5-methyl-5*H*-furan-2-one (10)

Lactone (**9**) (350 mg, 1.70 mmol) in Ph_2O (3.0 mL) was sonicated under bubbling of argon gas for 30 min and then the solution was refluxed for 2 h. The mixture was directly chromatographed (silica gel: 10 g,

eluent: AcOEt/hexane = 1:5) to give the butenolide (**10**) (178 mg, 76%) as a colorless oil. The optical purity of **10** was determined to be >98% ee by HPLC with a chiral stationary phase (Chiralcel OD; eluent: 2-propanol/hexane = 1:9).

10: $[\alpha]_D^{20}$ +21.3° (*c* 0.62, $CHCl_3$). IR (film): ν 1756 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.47 (3H, s), 2.50 (2H, d, *J* = 7.4 Hz), 5.08-5.17 (2H, m), 5.60-5.76 (1H, m), 6.03 (1H, d, *J* = 5.6 Hz), 7.35 (1H, d, *J* = 5.6 Hz). ^{13}C NMR ($CDCl_3$) δ 23.3, 40.2, 90.2, 119.7, 121.2, 130.7, 158.8, 173.1. EIMS: *m*/*z* 138 (M^+), 41 (100 %). HRMS: calcd for $C_8H_{10}O_2$ 138.1554. Found 138.1566.

(5*R*)-5-Allyl-5-methyldihydrofuran-2-one [(–)-7]

To a stirred suspension of CuI (168 mg, 0.88 mmol) in THF (2.4 mL) and HMPA (0.6 mL) was added DIBALH (0.90 mL, 0.95 M in hexane, 0.88 mmol) at –78 °C. The solution was stirred for 1 h, then the butenolide (**10**) (110 mg, 0.80 mmol) in THF (1.5 mL) was added, and the whole mixture was stirred for 0.5 h at the same temperature. Sat. aq. NH_4Cl was added to the mixture to quench the reaction. This mixture was extracted with ether. The combined organic layer was washed with sat. aq $NaHCO_3$ and brine, then dried over $MgSO_4$. The organic layer was evaporated under reduced pressure and the residue was chromatographed (silica gel: 6 g, eluent: AcOEt/hexane = 1:4) to give the lactone [(–)-**7**] (91 mg, 81%) as a colorless oil.

(–)-**7**: $[\alpha]_D^{21}$ –3.6° (*c* 1.0, CH_3OH), lit.,[12e] $[\alpha]_D^{17}$ +3.33° (*c* 1.27, CH_3OH). IR (film): ν 1773 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (3H, s), 1.95 (1H, ddd, *J* = 12.9 Hz, 9.1 Hz, 7.4 Hz), 2.16 (1H, ddd, *J* = 12.9 Hz, 8.7 Hz, 8.2 Hz), 2.42 (2H, d, *J* = 7.2 Hz), 2.56-2.63 (2H, m), 5.13-5.20 (2H, m), 5.71-5.87 (1H, m). ^{13}C NMR ($CDCl_3$) δ 26.0, 29.1, 32.1, 45.1, 85.8, 119.5, 131.8, 176.3. EIMS: *m*/*z* 140 (M^+), 99 (100 %). HRMS: calcd for $C_8H_{12}O_2$ 140.0837. Found 140.0834.

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