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Concise enantiodivergent synthesis of (+)- and (−)-*trans*-quercus lactones

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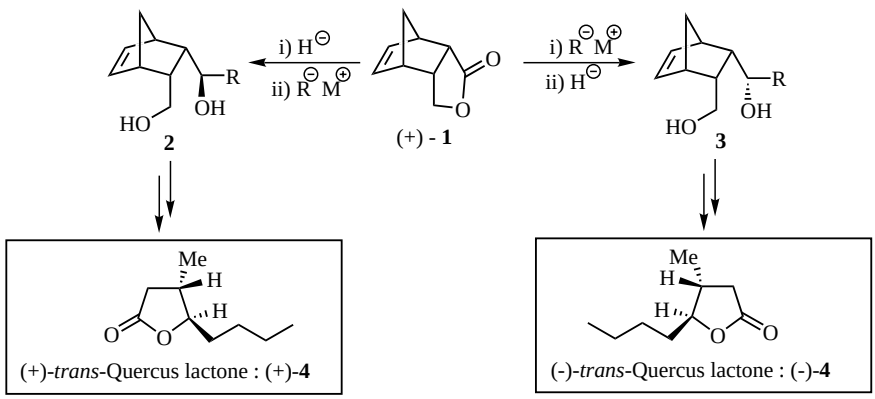
Abstract—A concise enantiodivergent total synthesis of (+)- and (−)-quercus lactones from the known tricyclic lactone (+)-**1** as a single chiral template was achieved using the diastereoselective nucleophilic addition of organometallic reagents as the key step.

1. Introduction

γ-Butyrolactones can be found as important constituents in many natural products.[1] Therefore, the asymmetric synthesis of γ-butyrolactone has been an ongoing challenge for researchers attempting the organic synthesis of certain substances.[2] We recently determined that the nucleophilic addition of hydride and organometallic reagents to racemic tricyclic lactone (±)-**1** could be highly diastereoselective and yield diastereomeric diols **2** and **3**,[3] respectively, depending on reaction conditions. We report herein an application of this methodology to synthesize chiral γ-butyrolactones and to effect the enantiodivergent synthesis of (+)- and (−)-*trans*-quercus lactones (also known as whisky lactone) **4** using chiral γ-substituted butenolide as the key intermediate (Scheme 1). (+)-*trans*-Quercus lactone **4** was isolated together with a *cis*-(−)-isomer from oak woods and aged spirits.[4] The *trans*-configuration of the methyl and butyl groups has been determined by ^{1}H NMR spectroscopy, and its absolute configuration has been assigned on the basis of an empirical correlation.[5] Many syntheses of **4**, including enantiodivergent routes, have been reported.[6,7]

2. Results and discussion

Chiral bicyclic lactone (+)-**1**,[8] which was prepared in enantiomerically pure form from D-mannitol,[8b] was partially reduced with diisobutylaluminum hydride (DIBAL) in tetrahydrofuran (THF) to give the lactol



Scheme 1.

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intermediate, followed by the addition of *n*-butylmagnesium chloride in the same flask, resulting in diol **5** in 82% yield with >99% d.e. On the other hand, a stoichiometric amount of *n*-butyllithium was added to (+)-**1** in toluene to give the ketone, followed by the addition of L-Selectride™, in one pot, which furnished diol **6** in 78% yield with >99% d.e. as determined by ^{1}H NMR, on the basis of the chemical shifts of the oxymethine proton of **5** (δ 3.65) and **6** (δ 3.69). In the latter case, when THF and DIBAL were used as the solvent and hydride source, respectively, we observed a lower yield and diastereoselectivity of **6** (38% yield, 4% d.e.).[9] Oxidation with a catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP) in the presence of 4-methylmorpholine *N*-oxide (NMO) gave the corresponding diastereomeric lactone **7** in 66% yield from **5**, and **8** in 61% yield from **6**, respectively.[10] Retro-Diels–Alder reaction in refluxing *o*-dichlorobenzene (ODCB) yielded the known enantiomeric 4-butyl-substituted butenolides (−)-**9** and (+)-**9**, which were the key intermediates in previous quercus lactone syntheses.[8c,e,j] The enantiomeric excess of **9** was determined by HPLC with a chiral column, [(−)-**9**: 90% e.e., and (−)-**9**: 92% e.e.]. This observed decrease in enantiomeric purity was probably the result of the partial enolization of **9**, which occurred via retro-Diels–Alder reaction. Stereoselective 1,4-addition of dimethylcuprate in diethyl ether, which has been reported previously,[8c] gave (+)-**4** in 72% yield from (−)-**9**, and (−)-**4** in 61% yield from (+)-**9**, respectively (Scheme 2).

We believe that the diastereoselectivity in the case of continuous nucleophilic addition can be explained as follows. First, nucleophilic addition to (+)-**1** gives the corresponding acetal derivative **10**, which equilibrates to the metal-chelated intermediate **11**. A second nucleophile then approaches from the outside of the chelate-ring to give the single diastereomer. Thus, the configuration of the newly generated stereocenter was controlled by the order in which the nucleophilic reagents were added (Scheme 3).

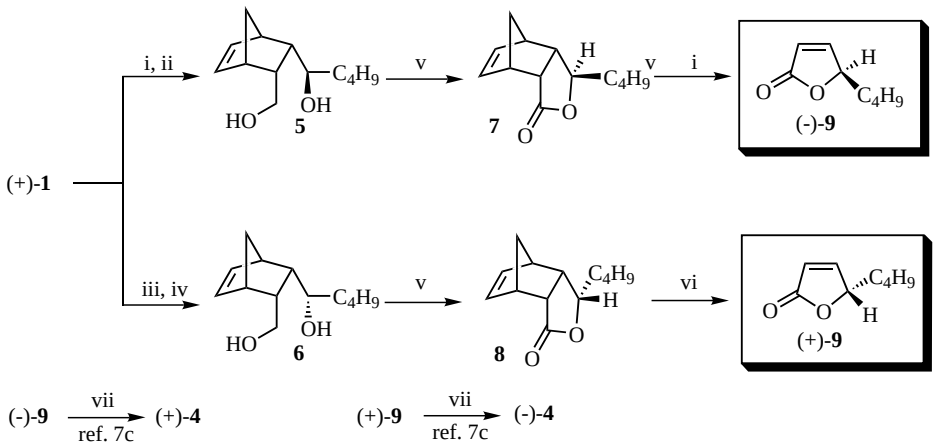
3. Conclusion

In conclusion, we have achieved a concise enantiodivergent total synthesis of (+)- and (−)-quercus lactones from (+)-**1**. This synthesis suggests that (+)-**1** was the synthetic equivalent of a chiral γ-substituted butyrolactone in both enantiomeric forms. On the basis of this concept, we have begun to investigate the chiral syntheses of versatile γ-substituted butyrolactone in enantiodivergent ways.

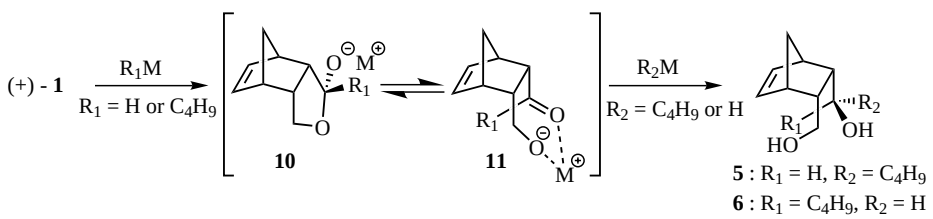
4. Experimental

4.1. General procedure

Melting points are uncorrected. IR spectra were recorded on a JASCO-FT-IR-5000 spectrometer. ^{1}H NMR spectra were recorded on a JEOL-GSX-270 (270



Scheme 2. *Reagents and conditions*: (i) DIBAL, THF, −78°C; (ii) *n*-butylmagnesium chloride, THF, −78°C (82% from **1**); (iii) 1.0 equiv. *n*-butyllithium, toluene, −78°C; (iv) L-Selectride, toluene, −78°C; (78% from **1**); (v) cat. TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2 (66% for **7**, 61% for **8**); (vi) ODCB, reflux [85% for (−)-**9**, 84% for (+)-**9**]; (vii) methyllithium, CuI, diethyl ether, −78°C [72% for (+)-**4**, 61% for (−)-**4**].



Scheme 3.

MHz) spectrometer. Mass spectra were recorded on a JEOL-DX-303 spectrometer. Enantiomeric excesses were determined on a Waters-HPLC 600 instrument equipped with a chiral column. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter.

4.2. (1*R*)-1-[(2′*S*,3′*R*)-3-Hydroxymethylbicyclo[2.2.1]-hept-5-en-2-yl]pentan-1-ol 5

To a stirred solution of (+)-**1** (100 mg, 0.67 mmol) in THF (4 mL) was added a solution of DIBAL (0.94 M in hexane, 0.80 mL, 0.73 mmol) at −78°C. The mixture was stirred at the same temperature for 1.5 h, *n*-butylmagnesium chloride (0.90 M in THF, 4.10 mL, 3.67 mmol) was added and the resulting mixture stirred at the same temperature for 5 h. Saturated aq. NH_4Cl (1.5 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (AcOEt, 3×15 mL), washed with satd aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (benzene/AcOEt = 4: 1) to give **5** as a colorless oil (115 mg, 82%). Compound **5**: $[\alpha]_D^{18} = +76.2$ (*c* 1.00, $CHCl_3$). IR (film): $\nu = 3254$, 2962, 1040, 729 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.94 (3H, t, $J = 7.1$ Hz), 1.30–1.53 (7H, m), 1.62–1.67 (1H, m), 2.27 (1H, ddd, $J = 10.3$, 8.0, 3.5 Hz), 2.49–2.59 (1H, m), 2.69 (2H, br s, exchangeable with D_2O), 2.78–2.83 (2H, m), 3.35–3.47 (2H, m), 3.65 (1H, dd, $J = 11.4$, 3.1 Hz), 6.01–6.06 (2H, m). ^{13}C NMR (270 MHz, $CDCl_3$): δ 14.1, 22.8, 27.1, 35.8, 45.9, 46.5, 46.9, 49.4, 49.6, 63.7, 71.8, 134.2, 135.3. EIMS: $m/z = 210$ (M^+), 67 (100%). HRMS: calcd for $C_{13}H_{22}O_2$ 210.1620, found 210.1598

4.3. (1*S*)-1-[(2′*S*,3′*R*)-3-Hydroxymethylbicyclo[2.2.1]-hept-5-en-2-yl]pentan-1-ol 6

To a stirred solution of (+)-**1** (700 mg, 4.67 mmol) in anhydrous toluene (40 mL) was added *n*-butyllithium (2.46 M in hexane, 2.00 mL, 5.13 mmol) at −78°C. The mixture was stirred at the same temperature for 2 h, and treated with L-Selectride™ (1.00 M in THF, 9.30 mL, 9.33 mmol) to it. The resulting mixture was stirred at the same temperature for 2.5 h. Then 10% aq. NaOH (5 mL) and 30% aq. hydrogen peroxide (3.5 mL) were added to quench the reaction. The mixture was extracted with AcOEt (3×20 mL), washed with brine (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt = 4: 1) to give **6** as colorless crystals (768 mg, 78%). Compound **6**: mp 97–98°C. $[\alpha]_D^{22} = -8.2$ (*c* 0.99, $CHCl_3$). IR (film): $\nu = 3288$, 2926, 1460, 1023, 1004 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.90 (3H, t, $J = 7.3$ Hz), 1.26–1.59 (8H, m), 2.24–2.31 (1H, m), 1.71 (2H, brs, exchangeable with D_2O), 2.37–2.47 (1H, m), 2.98 (1H, brs), 3.02 (1H, brs), 3.34–3.48 (2H, m), 3.69 (1H, dd, $J = 10.8$, 5.3 Hz), 6.18–6.26 (2H, m). ^{13}C NMR (270 MHz, $CDCl_3$): δ 14.1, 22.7, 28.6, 38.2, 45.1, 45.2, 45.6, 49.0, 49.3, 63.1, 71.5, 135.5. EIMS: $m/z = 210$ (M^+), 66 (100%). HRMS: calcd for $C_{13}H_{22}O_2$ 210.1620 found 210.1594.

4.4. (2*R*,5*R*,6*S*)-5-Butyl-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one 7

To a stirred solution of **5** (95 mg, 0.45 mmol) in anhydrous CH_2Cl_2 (5 mL) was added 4 Å molecular sieves (crushed and dried, 452 mg), NMO (158 mg, 1.36 mmol), and TPAP (8.0 mg, 0.02 mmol) at 0°C. The mixture was stirred at rt for 3 h and 10% aq. $NaHSO_3$ (4 mL) was added to quench the reaction. After filtration on a Celite pad, the filtrate was extracted with CH_2Cl_2 (3×15 mL), washed with 10% aq. HCl (10 mL), satd aq. $NaHCO_3$ (10 mL), and brine (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt = 15: 1) to give **7** as a colorless oil (61 mg, 66%). Compound **7**: $[\alpha]_D^{19} = -30.7$ (*c* 0.95, $CHCl_3$). IR (film): $\nu = 2938$, 1764, 1183 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.91 (3H, t, $J = 7.0$ Hz), 1.31–1.44 (5H, m), 1.55–1.69 (3H, m), 2.72 (1H, td, $J = 9.2$, 4.0 Hz), 3.08–3.09 (1H, m), 3.24–3.33 (2H, m), 3.91 (1H, dt, $J = 6.7$, 3.3 Hz), 6.24 (1H, dd, $J = 5.7$, 3.0 Hz), 6.30 (1H, dd, $J = 5.7$, 3.0 Hz). ^{13}C NMR (270 MHz, $CDCl_3$): δ 14.0, 22.5, 27.0, 36.7, 45.6, 46.2, 46.7, 48.5, 51.7, 82.9, 134.9, 136.7, 177.9. EIMS: $m/z = 206$ (M^+), 66 (100%). HRMS: calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1320.

4.5. (2*R*,5*S*,6*S*)-5-Butyl-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one 8

To a stirred solution of **6** (768 mg, 3.66 mmol) in anhydrous CH_2Cl_2 (10 mL) was added 4 Å molecular sieves (crushed and dried, 3.65 g), NMO (1.29 g, 10.97 mmol), and TPAP (64 mg, 0.18 mmol) at 0°C. The mixture was then stirred at rt for 3 h. 10% Aq. $NaHSO_3$ (4 mL) was added to quench the reaction. After filtration on a Celite pad, the filtrate was extracted with CH_2Cl_2 (3×20 mL), washed with 10% aq. HCl (20 mL), satd aq. $NaHCO_3$ (20 mL), and brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt = 10: 1) to give **8** (463 mg, 61%) as a colorless oil. Compound **8**: $[\alpha]_D^{19} = -104.3$ (*c* 1.04, $CHCl_3$). IR (film): $\nu = 2960$, 1763, 1187 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.92 (3H, t, $J = 7.3$ Hz), 1.30–1.77 (8H, m), 2.99–3.08 (2H, m), 3.25–3.29 (1H, m), 3.39 (1H, dd, $J = 8.8$, 4.9 Hz), 4.41–4.49 (1H, m), 6.20–6.21 (2H, m). ^{13}C NMR (270 MHz, $CDCl_3$): δ 13.9, 22.5, 28.8, 31.0, 44.7, 44.9, 45.2, 48.6, 52.7, 81.5, 135.0, 135.7, 177.8. EIMS: $m/z = 206$ (M^+), 66 (100%). HRMS: calcd for $C_{13}H_{18}O_2$ 206.1307 found 206.1316.

4.6. (*R*)-5-Butyl-2(5*H*)-furanone (−)-9

A solution of **7** (340 mg, 1.65 mmol) in ODCB (24 mL) was sonicated under bubbling of argon gas for 20 min. The mixture was stirred under reflux for 20 h. After cooling, the mixture was directly chromatographed on silica gel (hexane/AcOEt = 3: 1) to give (−)-**9** (197 mg, 85%) as a colorless oil. Compound (−)-**9**: $[\alpha]_D^{21} = -90.3$ (*c* 0.84, $CHCl_3$), lit.:[8c] $[\alpha]_D^{21} = -101.0$ ($CHCl_3$). IR (film): $\nu = 2962$, 2938, 1752, 1163 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.92 (3H, t, $J = 7.1$ Hz), 1.33–1.50 (4H, m), 1.61–1.85 (2H, m), 5.01–5.07 (1H, m), 6.11 (1H, dd,

$J=5.7$, 2.0 Hz), 7.45 (1H, dd, $J=5.8$, 1.5 Hz). ^{13}C NMR (270 MHz, $CDCl_3$): δ 13.8, 22.4, 27.1, 32.9, 83.4, 121.6, 156.3, 173.2. EIMS: $m/z=140$ (M^+), 84 (100%). HRMS: calcd for $C_8H_{12}O_2$ 140.0837, found 140.0862.

The enantiomeric purity was determined to be 90% e.e. by HPLC using a column with a chiral stationary phase [Chiralcel OD, ^{i}PrOH/hexane = 1/9].

4.7. (*S*)-5-Butyl-2(5*H*)-furanone (+)-9

In the same manner as described for (−)-**9**, **8** gave (+)-**9** (159 mg, 84%) as a colorless oil. Compound (+)-**9**: $[\alpha]_D^{21}=+91.6$ (c 1.01, $CHCl_3$). Spectroscopic data were identical with those of (−)-**9**. The enantiomeric purity was determined to be 90% e.e. by HPLC using a chiral column as above.

4.8. (+)-*trans*-Quercus lactone (+)-4

To a stirred suspension of copper(I) iodide (1.34 g, 7.05 mmol) in anhydrous diethyl ether (Et_2O, 9 mL) was added methyllithium (1.14 M in Et_2O, 12.4 mL, 14.1 mmol) at −30°C. The mixture was stirred at the same temperature for 0.5 h, a solution of (−)-**9** (200 mg, 1.41 mmol) in Et_2O (14 mL) was added to the reaction mixture at −78°C, which was then stirred at the same temperature for 3.5 h. 10% Aq. HCl (15 mL) was added to quench the reaction. After filtration on a Celite pad, the filtrate was extracted with Et_2O (3×15 mL), washed with 28% aq. ammonia (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane/Et_2O = 3:1) to give (+)-**4** (158 mg, 72%) as a colorless oil. Compound (+)-**4**: $[\alpha]_D^{21}=79.9$ (c 1.01, CH_3OH), lit.:[6] for the natural (+) form, $[\alpha]_D^{15}=+79$ (c 1.04, CH_3OH). IR (film): $\nu=$ 2964, 2938, 1781 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.92 (3H, t, $J=6.9$ Hz), 1.14 (3H, d, $J=6.4$Hz), 1.29–1.73 (6H, m), 2.13–2.27 (2H, m), 2.60–2.75 (1H, m), 4.01 (1H, dt, $J=7.6$, 4.1 Hz). ^{13}C NMR (270 MHz, $CDCl_3$): δ 13.8, 17.5, 22.4, 22.8, 33.7, 36.0, 37.1, 87.4, 176.6. EIMS: $m/z=156$ (M^+), 99 (100%). HRMS: calcd for $C_9H_{16}O_2$ 156.1150, found 156.1176.

4.9. (−)-*trans*-Quercus lactone (−)-4

In the same manner as described for (+)-**4**, (+)-**9** gave (−)-**4** (28 mg, 61%) as a colorless oil. Compound (−)-**4**: $[\alpha]_D^{21}=-75.1$ (c 1.02, CH_3OH). Spectroscopic data were identical with those of (+)-**4**.

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