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Regioselective Synthesis of α-Methyl 2-Methyleneglutarate via a Novel Lactonization−Elimination Rearrangement

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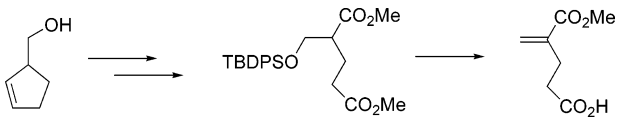
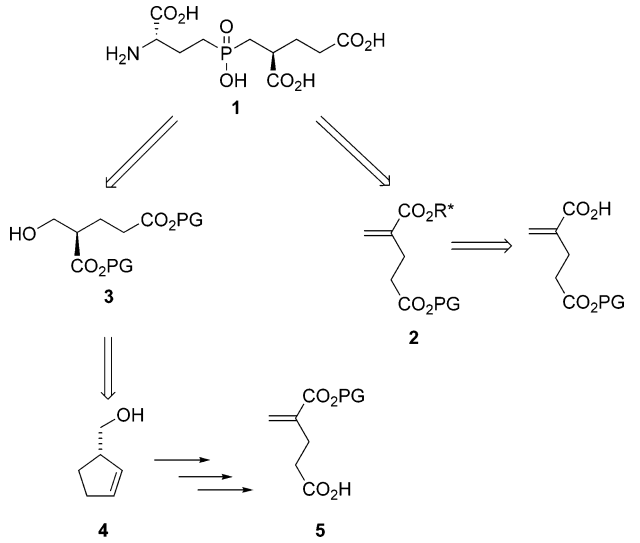


A facile route to the α-methyl ester of 2-methyleneglutarate via a three-step sequence from 3-hydroxymethylcyclopentene is described. Regioselective formation of the monoacid from a diester precursor proceeds via a novel fluoride-mediated, tandem deprotection/rearrangement of *O*-silyl 2-(hydroxymethyl)dimethylglutarate.

Acrylic acids and acrylate esters substituted at C-2 are synthetically useful intermediates, particularly in the synthesis of natural products,[1−3] pseudopeptides,[4−6] and polymers.[7] Our interest in the design of phosphorus-containing pseudopeptides as inhibitors of ATP-dependent ligases[8,9] and Zn proteases[10] has led us to develop new routes to both the α- and γ-monoesters of 2-methyleneglutaric acid. As shown in Scheme 1, retrosynthetic analysis suggested that the desired pseudopeptide, **1**, could possibly be obtained by either of two routes. These included the stereoselective conjugate addition of a nucleophilic organophosphorus synthon to the differentially protected α-methyleneglutarate, **2**, bearing a chiral auxiliary (e.g., Evans' oxazolidinone).[5] In our hands, the diastereoselectivity of this reaction was modest,[9] so the possible use of Δ^2-cyclopentenylcarbinol, **4**, as a glutarate surrogate leading to (2*R*)-2-(hydroxymethyl)glutaric acid, **3**, was investigated

SCHEME 1



Racemic **4** (*rac*-**4**) and its sulfonate esters have been investigated as precursors of delocalized carbonium ions, leading to rearranged products on solvolysis.[11] These authors reported a multistep, low-yielding synthesis of *rac*-**4**, which has been used by at least one other group but with no yields given.[12] To synthesize pseudopeptide **1** with the desired stereochemistry (2*S*,2′*S*), a stereospecific synthesis of **3** was required which, in turn, required a substituted cyclopentene precursor, e.g., **4**, of high stereochemical purity. The enantiomer of **4**, (3*R*)-3-(hydroxymethyl)cyclopentene (*ent*-**4**), has been described by Maeda and Inouye.[13] Thus, *ent*-**4** was obtained from ethyl (2-oxo)cyclopentane carboxylate via an enzyme-catalyzed dynamic kinetic resolution to yield the (2*R*)-2-hydroxy ester, followed by xanthate formation, pyrolytic elimination to form the cyclic olefin, and finally reduction of the carboxylic acid ester to yield *ent*-**4**. This compound is readily synthesized in high yield and in large quantities if desired (see the Supporting Information for details). To investigate the synthetic method outlined in Scheme 1, ent-**4**, which is much more readily accessible than **4**,[9] was used in the research described in this paper.

Protection of the alcohol as the *O*-silyl ether followed by oxidative ring opening and concomitant methyl esterification with the method of Marshall and Garafalo[14] provided a mixture of mono- and diesters. Following treatment with $TMSCHN_2$, diester **7** was obtained in 70% yield (Scheme 2). At this point, the strategy was to remove the silyl ether (**7** → **3**) in order to incorporate various phosphorus functionalities, which would be converted to a nucleophilic reagent (P^{III} species, phosphorus anion, phosphorus radical) for construction of the second P−C bond required in the synthesis of **1**. To our surprise, treatment of **7** with TBAF resulted in a novel deprotection−rearrangement reaction to give **5** in 84% yield.

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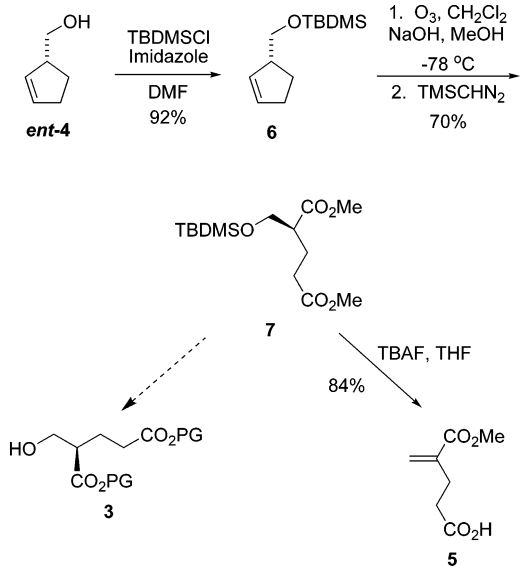
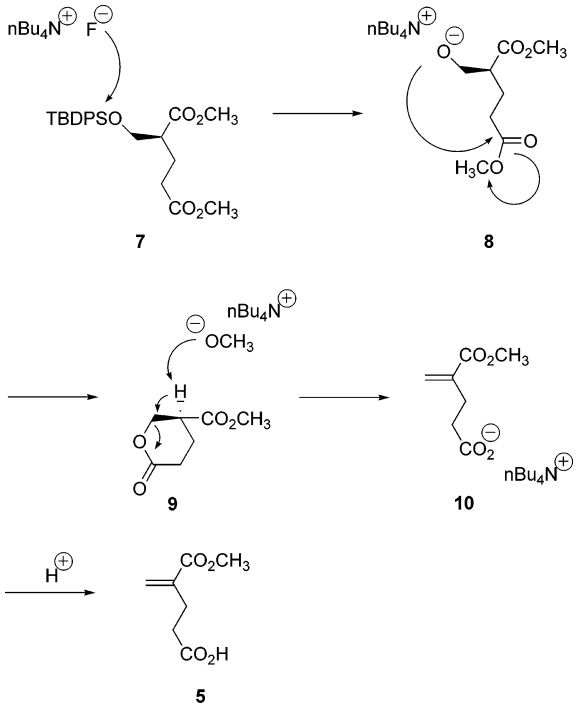
SCHEME 2



Formation of **5** can be rationalized by the mechanism shown in Scheme 3. Deprotection of the silyl protecting group results in formation of alkoxide **8**, which attacks the γ-methyl ester to form lactone **9** and generate 1 equiv of methoxide anion. The methoxide anion then abstracts the acidic lactone methine proton, generating compound **10**, which upon workup provides **5** in excellent yield. To our knowledge this is the first time that this type of rearrangement has been described in the literature.

While synthetic routes to both 2-methylene glutaric acid and the corresponding diesters are readily available,[4,15−21] selective esterification of one of the two acids has been reported only rarely. 2-Methyleneglutaric acid 1-methyl ester, **5**, has been reported in a mechanistic study on the photooxygenation of 2-methoxy-3-methyl-2-cyclopenen-1-one;[22] however, the isolated yield was not reported and NMR analysis of the crude reaction indicates yields of less than 50% for the formation of **5**. The corresponding α-ethyl ester has been reported in the patent literature via a lipase-catalyzed de-esterification of diethyl 2-methyleneglutarate.[23] The regioisomeric ester, 2-methyleneglutaric acid 5-methyl ester, has been prepared electrochemically by the addition of CO_2 to pent-4-ynoic acid methyl ester in 38% yield; however, the free acid was not isolated. Instead, the product was converted to the dimethyl ester for isolation and purification.[24] As reported in the patent literature, this regioisomer has also been synthesized via an iodine-mediated selective esterification of the nonconjugated carboxylic acid of 2-methyleneglutaric acid.[25] We recently described an efficient synthesis of 2-methylene glutaric acid 5-*tert*-butyl ester through Michael addition of protected malonates to *tert*-butyl acrylate followed by a tandem Mannich reaction and in situ decarboxylation.[9]

SCHEME 3



The efficient synthesis of **5** described herein uses an enantiomerically pure 3-substituted cyclopentene, *ent*-**4**, for the reasons described above. However, since the chirality at the stereogenic center is lost during the rearrangement to form **5**, possible use of a racemic precursor, *rac*-**4**, that may be more readily available was investigated. In addition to the syntheses of *rac*-**4** noted above, a low-yielding multistep synthesis of racemic *rac*-**4** has been reported[26] via LAH reduction of the corresponding carboxylic acid which, in turn, was generated from the addition of CO_2 to the Grignard reagent of 3-chlorocyclopentene. In our hands, the yield of this Grignard reaction was extremely low. A higher yielding preparation of racemic *rac*-**4** using Rieke magnesium has been reported,[27] but the use of highly flammable Rieke magnesium for the large-scale preparation of *rac*-**4** is of concern. Since a search of the literature and our own experience did not produce an efficient synthesis of *rac*-**4**, the use of *ent*-**4** as described (Scheme 2) is recommended.

In summary, a concise 3-step synthesis of an α-protected methyleneglutarate **5** from easily prepared starting materials has been developed. This compound is a useful precursor for the synthesis of peptidomimetic compounds and may be useful as intermediates for synthesizing partially or fully reduced functionalities, i.e., aldehyde or alcohol, at the γ-position of 2-methyleneglutarate.

Experimental Section

General Experimental Procedures. See the Supporting Information.

(*R*)-1- *tert*-Butyldimethylsilyloxymethylcyclopent-2-ene, 6. To a solution of *ent*-**4**[13] (0.9 g, 9.2 mmol) and TBDMSCl (2.8 g, 18.4

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mmol) in anhydrous DMF (10 mL) at room temperature under Ar was added imidazole (3.1 g, 46 mmol) in one portion. The reaction was stirred at room temperature for 24 h. The reaction was concentrated under reduced pressure (2 mmHg, 40 °C) and the crude oil was partitioned between hexanes/Et_2O (1:1, 100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with hexanes/Et_2O (1:1, 50 mL) and the combined organic layers were washed with H_2O (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (4:1 hexanes/EtOAc) to give 1.8 g of **6** as a clear oil (92%). ^{1}H NMR ($CDCl_3$) δ 5.77 (m, 1H), 5.69 (m, 1H), 3.48 (m, 2H), 2.86 (m, 1H), 2.30 (m, 2H), 1.96 (m, 1H), 1.52 (m, 1H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 132.5, 132.0, 67.4, 48.9, 32.0, 26.3, 26.1, 18.5, −5.1. MS (ESI) *m*/*z* 212.2 ([M + H]$^+$, 100). HRMS (ESI) calcd for $C_{12}H_{24}OSi$ 212.1596 [M + H]$^+$, found 212.1593.

(*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)pentanedioic Acid Dimethyl Ester, 7. Ozone was bubbled through a solution of **6** (1.0 g, 4.7 mmol) in 2.5 M NaOH in MeOH (10 mL) and CH_2Cl_2 (40 mL) at −78 °C until a persistent blue color of excess ozone was observed. O_2 was bubbled through the solution for 20 min to purge the excess ozone. The reaction was allowed to warm to room temperature and was partitioned between diethyl ether (25 mL) and H_2O (25 mL). The aqueous layer was extracted with diethyl ether (3 × 25 mL). The organic layer was concentrated and the crude oil was taken up in EtOAc (25 mL), dried over Na_2SO_4, filtered, and concentrated. The resulting clear oil was dissolved in MeOH (10 mL), cooled to 0 °C, and treated with $TMSCHN_2$ until a persistent yellow color was observed. The ice bath was removed and the reaction was stirred at room temperature for 15 min, then quenched with AcOH and concentrated. The crude product was purified by silica gel chromatography (4:1 hexanes/EtOAc) to give 0.98 g of **7** as a clear oil (70%). ^{1}H NMR ($CDCl_3$) δ 3.77 (m, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 2.61 (m, 1H), 2.36 (m, 2H), 1.90 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 174.4, 173.6, 64.0, 51.75, 51.72, 47.7, 31.8, 25.9, 23.7, 18.3, −5.4. MS (ESI) *m*/*z* 304.2 ([M + H]$^+$, 100). HRMS (ESI) calcd for $C_{14}H_{28}O_5Si$ 304.1706 [M + H]$^+$, found 304.1704.

2-Methylenepentanedioic Acid 1-Methyl Ester (α-Methyl 2-Methyleneglutarate), 5. To a solution of **7** (0.75 g, 2.5 mmol) in anhydrous THF (10 mL) at 0 °C was added TBAF (3.8 mL, 3.8 mmol). The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was concentrated and the crude oil was portioned between EtOAc (50 mL) and 1% aq HCl (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (1:1 hexanes/EtOAc then 100% EtOAc) to give 0.33 g of **5** as a clear oil (84%). ^{1}H NMR ($CDCl_3$) δ 9.41 (br s, 1H), 6.21 (d, 1H, J = 1.1 Hz), 5.62 (d, 1H, J = 1.1 Hz), 3.75 (s, 3H), 2.63 to 2.53 (overlapping m, 4H). ^{13}C NMR ($CDCl_3$) δ 178.8, 167.2, 138.6, 126.3, 52.1, 33.0, 27.1. MS (CI/NH_3) *m*/*z* 159.1 ([M + H]$^+$, 100). HRMS (CI/NH_3) calcd for $C_7H_{11}O_4$159.1623 [M + H]$^+$, found 159.0656.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data for compounds **5**−**7** and experimental procedures for the large-scale synthesis of *ent*-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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