Practical Synthesis of Chiral Synthons for the Preparation of HMG-CoA Reductase Inhibitors

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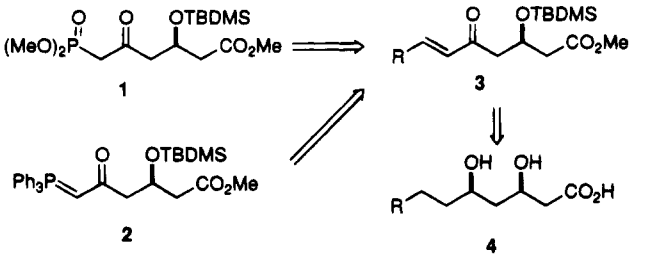
A practical procedure for the enantioselective preparation of optically pure (*R*)- and (*S*)-monomethyl esters of 3-[(*tert*-butyldimethylsilyl)oxy]pentanedioic acid has been developed by diastereoselective ring-opening of 3-[(*tert*-butyldimethylsilyl)oxy]pentanedioic anhydride **5** by benzyl (*R*)- and (*S*)-mandelate, respectively. These half-esters afforded chiral Wittig reagent **2** and Horner–Wadsworth–Emmons (HWE) reagent **1** efficiently which have been proved to be useful in the synthesis of HMG-CoA reductase inhibitors. The method is applied to the synthesis of the (*R*)-3-methylglutaric acid, monomethyl ester.

Since the recognition of hypercholesterolemia as a primary risk factor of atherosclerosis and coronary heart disease,[1] intense efforts have been made to identify the chemical entity that is capable of regulating the plasma level of this sterol. These efforts resulted in the discovery of compactin and mevinolin,[2] two potent inhibitors of cholesterol biosynthesis at the level of the rate-limiting enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Comparison of compactin, mevinolin, and other known HMG-CoA reductase (HMGR) inhibitors revealed that the 3,5-dihydroxyheptanoic acid moiety **4** is present in all compounds, and it is well-documented that this group represents a pharmacophore for HMGR inhibitor recognition. There have been many reports on the synthetic methods of this functional group.[3]

Heathcock and co-workers have demonstrated the utility of the optically active Horner–Wadsworth–Emmons (HWE) reagent **1**[4] in their synthesis of compactin and its analogues. This synthon allows for the direct introduction of a highly functionalized side chain keto-ester **3**, which eventually leads to the chiral 3,5-dihydroxyheptanoic acid moiety **4** essential for HMGR inhibition activity (Scheme 1). They reported two routes to HWE reagent **1** that relied on the highly diastereoselective reaction[5] of commercially available prochiral anhydride **5** with either (*R*)-1-phenylethanol or (*S*)-1-(1′-naphthyl)ethanol for the introduction of asymmetry (88–95% diastereomeric excess (de)). Subsequent transformations gave HWE reagent **1** in moderate yield. The same reagent **1** was prepared by Karanewsky and co-workers[6] lately by using a similar desymmetrization strategy. They employed (*S*)-1-phenethylamine for diastereoselective ring-opening of anhydride **5** (58% de). Although these syntheses have been used to prepare **1** in multigram quantities, they still have some drawbacks. The cost and availability of the chiral auxiliary, 1-arylethanol, in enantiomerically pure form limit the preparative utility of Heathcock's method, and the hazardous reagents such as diazomethane and dinitrogen tetroxide in the Karanewski's synthesis hampered the general use of reagent **1**.

Scheme 1



During our investigations directed toward the syntheses of mevinolin derivatives and structurally simplified HMGR inhibitors, we desired a safer and more practical procedure of HWE reagent **1** or chiral synthons applicable for the synthesis of the chiral 3,5-dihydroxyheptanoic acid side chain **4** of HMGR inhibitors. In contrast to the established utility of HWE reagent **1** the corresponding Wittig reagent **2** was unknown and we focused on the exploration of **2** because it is expected to condense with aldehydes under neutral conditions and was found useful in the preparation of compounds[7] which are unstable under the basic conditions required for HWE reagent **1**. Here, we describe a practical enantioselective synthesis of 3-hydroxyglutaric acid half esters[8] (*R*)- and (*S*)-**8** and further conversion to chiral Wittig reagent **2** and HWE reagent **1**. Our method offers practical routes for the large scale synthesis of useful synthons for HMGR inhibitors.[9]

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(1) Endo, A. *J. Med. Chem.* **1985**, *28*, 401.

(2) Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.

(3) Recent references. McCague, R.; Olivo, H. F.; Roberts, S. M. *Tetrahedron Lett.* **1993**, *34*, 3785. Minami, T.; Takahashi, K.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 513. T. Valverde, S.; Lopez, J. C.; Gomez, A. M.; Garcia-Ochoa, S. *J. Org. Chem.* **1992**, *57*, 1613. Reddy, G. B.; Minami, T.; Hanamoto, T.; Hiyama, T. *J. Org. Chem.* **1991**, *56*, 5752. Bonini, C.; Pucci, P.; Viggiani, L. *J. Org. Chem.* **1991**, *56*, 4050. Wess, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstein, G.; Kleine, H.; Schnierer, M. *Tetrahedron Lett.* **1990**, *31*, 2545. Prasad, K.; Chen, K.-M.; Repic, O.; Hardtmann, G. E. *Tetrahedron: Asymmetry* **1990**, *1*, 703. Boquel, P.; Chapleur, Y. *Tetrahedron Lett.* **1990**, *31*, 1869. Sit, S. Y.; Parker, R. A.; Motoc, T.; Han, W.; Balasubramanian, N.; Catt, J. D.; Brown, P. J.; Harte, W. E.; Tompson, M. D.; Wright, J. J. *J. Med. Chem.* **1990**, *33*, 2982. David, C.; Gesson, J. P.; Jacquesy, J. C. *Tetrahedron Lett.* **1989**, *30*, 6015.

(4) (a) Rosen, T.; Watanabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657. (b) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731. (c) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374.

(5) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142.

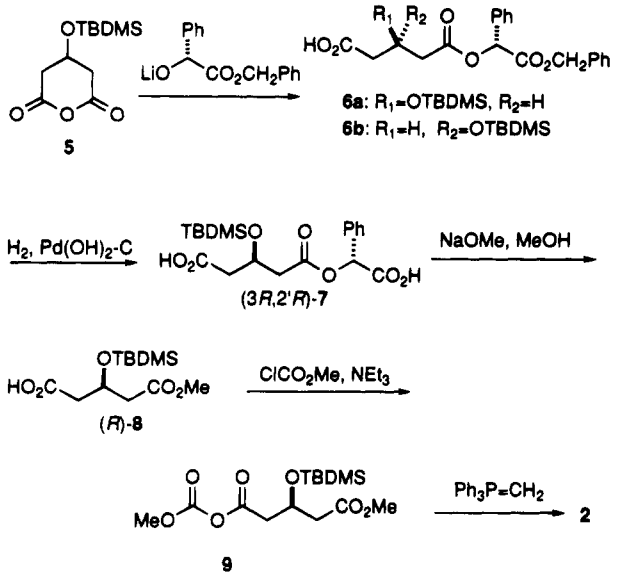
(6) Karanewsky, D. S.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1991**, *56*, 3744.

(7) (a) Konoike, T.; Araki, Y. PCT Int. Appl., WO 92/22560, 1992. (b) Hirai, K.; Ishiba, T.; Koike, H.; Watanabe, M. European Application EP-A-0464845, 1992. (c) Hirai, K.; Ishiba, T.; Koike, H.; Watanabe, M. Jpn Kokai Tokkyo Koho JP 04,352,767 [92,352,767], 1992.

(8) Monteiro, J.; Braun, J.; Goffic, F. L. *Synth. Commun.* **1990**, *20*, 315.

0022-3263/94/1959-7849$04.50/0

Scheme 2



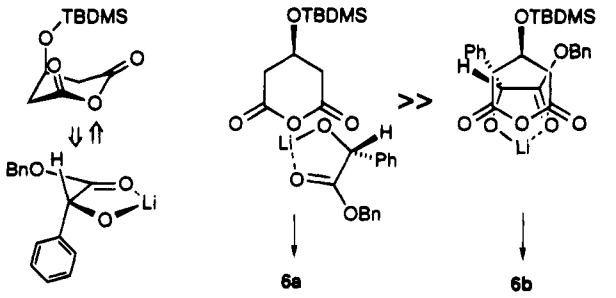
Results and Discussion

Previous reports[10] from our laboratories described the chiral synthesis of the bicyclo[2.2.1]heptanedicarboxylic acid half esters. The feature of the asymmetric synthesis consists of desymmetrization of prochiral bicyclic anhydrides with the chiral mandelic esters. The chiral mandelates were highly effective chiral auxiliaries for the enantioselective fission of prochiral anhydrides, although they had rarely been used for the asymmetric synthesis[11] among a variety of chiral alcohols.[12] It was our interest to extend the synthetic utility of desymmetrization by the common mandelic esters by applying them to other prochiral anhydrides. To this end, we have evaluated the anhydride **5** for the reaction with chiral benzyl mandelate to obtain chiral 3-hydroxyglutaric acid half esters.

Enantioselective Ring-opening of Prochiral Anhydride 5. Scheme 2 shows the protocol developed for the synthesis of the chiral monomethyl ester (*R*)-**8**. In our primary study, we focused on benzyl (*R*)-(−)-mandelate as a chiral inducer and cleaved prochiral anhydride **5**. The reaction of anhydride **5** with the lithium salt of benzyl (*R*)-(−)-mandelate in THF at −78 °C gave a 9:1 mixture of diastereomeric acids **6a** and **6b** in essentially quantitative yield.

The conditions were surveyed to optimize the degree of chiral recognition in the reaction of anhydride **5** with benzyl (*R*)-mandelate. Other metal salts (Na, Mg, and Zn) did not improve the selectivity. Heathcock's condition

Scheme 3



(DMAP, −20 °C) gave a 1:1 mixture, and triethylamine under high pressure (9 kbar) showed the opposite selectivity (1:2). The ratio and the yield were sensitive to the reaction temperature, and the conversion was incomplete at −100 °C and the selectivity was lower (5:2) at −40 °C.

We also tried several other chiral hydroxy esters to improve the diastereoselectivity of the ring-opening and to overcome the undesired side reaction in the next deprotection of the benzyl ester. These included methyl mandelate, benzyl lactate, and benzyl hexahydromandelate,[13] but none of them showed practical benefits. Consequently, we chose benzyl mandelate as a chiral auxiliary because of availability and selectivity.

Scheme 3 shows the probable transition state assembly for the desymmetrization reaction. Preferential formation of 3*R*,2'*R* diastereomer **6a** was explained by considering the facial selectivity of both anhydride **5** and lithium salt of benzyl (*R*)-mandelate. Nagao and coworkers[14] reported an axial preference of the silyloxy group of anhydride **5** and it is reasonable that it is susceptible to nucleophilic attack from the opposite side of the silyloxy group. In the lithium-chelating structure of benzyl mandelate, the steric difference between the phenyl group and the hydrogen contributed to the face-selective attack to anhydride **5** from the side of hydrogen. The facial preference of the two substrates led to the transition state of the ring-opening as depicted in the left of Scheme 3. In terms of the regioselectivity for the ring-opening transition states that satisfy the facial preference, the two modes of ring-opening were conceptually possible. Among two transition states, the less crowded conformation of six- and five-membered rings (Scheme 3, center) seemed to be favorable over the other (Scheme 3, right) where two rings are overlapped.

We were unable to isolate optically pure **6a** from the crude mixture as a crystalline derivative. Thus, we explored a way to enhance the diastereomeric purity. The benzyl ester was removed by catalytic hydrogenolysis, followed by a simple purification of 3*R*,2'*R* dicarboxylic acid (3*R*,2'*R*)-**7** by crystallization from the mixture of (3*R*,2'*R*)-**7** and 3*S*,2'*R* diastereomer. Careful control of the reaction conditions was necessary in order to get dicarboxylic acid (3*R*,2'*R*)-**7** as an enantiomerically pure crystalline diastereomer. Over-reduction was a common side reaction, yielding 3-[(*tert*-butyldimethylsilyl)oxy]-pentanedioic acid and phenylacetic acid. These byproducts interfered with the purification of (3*R*,2'*R*)-**7**. We tried a variety of conditions to overcome the difficulties. A survey of catalysts and solvents showed that palladium

(9) Recent references. Jendralla, H.; Granzer, E.; Kerekjarto, B. v.; Krause, R.; Schacht, U.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Kesseler, K.; Wess, G.; Chen, L.-J.; Granata, S.; Herchen, J.; Kleine, H.; Schüssler, H.; Wagner, K. *J. Med. Chem.* **1991**, *34*, 2962. Roth, B. D.; Bocan, T. M. A.; Blankley, C. J.; Chuchowski, A. W.; Creger, R. S.; Creswell, M. W.; Ferguson, E.; Newton, R. S.; O'Brien, P.; Picard, J. A.; Roark, W. H.; Sekerke, C. S.; Sliskovic, D. R.; Wilson, M. W. *J. Med. Chem.* **1991**, *34*, 466. Blackwell, C. M.; Davidson, A. H.; Launchburry, S. B.; Lewis, C. N.; Morris, E. M.; Reeve, M. M.; Roffey, J. A. R.; Tipping, A. S.; Todd, R. S. *J. Org. Chem.* **1992**, *57*, 1935.

(10) (a) Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1991**, *56*, 2122. (b) Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1991**, *56*, 4120.

(11) (a) Walkup, R. D.; Obeyesekere, N. U. *J. Org. Chem.* **1988**, *53*, 923. (b) Morley, A. D.; Hollinshead, D. M.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1047.

(12) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935.

(13) Faunce, J. A.; Friebe, T. L.; Grisso, B. A.; Losey, E. N.; Sabat, M.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1989**, *111*, 4508.

(14) Nagao, Y.; Goto, M.; Ochiai, M.; Shiro, M. *Chem. Lett.* **1990**, 1503.

catalysts were the most satisfactory. However, they showed some degree of over-reduction. Employing dichloromethane or methanol as a solvent or higher pressure of hydrogen led to the extensive over-reduction. Further examination of the conditions indicated that consistent yield and purity of (3*R*,2′*R*)-**7** was achieved when the hydrogenolysis was terminated at the stage of ca. 0.9 equiv of hydrogen consumption. In practice, ethyl acetate (EtOAc) extracts of **6a** and **6b** were subjected to hydrogenolysis over Pearlman's catalyst to give a diastereomeric mixture of dicarboxylic acids. After aqueous workup to remove a small amount of unreacted **6a** and **6b,** an enantiomerically enriched diastereomer ((3*R*,2′*R*)-**7** (98% de)) was obtained by crystallization from toluene. A single recrystallization from EtOAc–toluene gave (3*R*,2′*R*)-**7** in 61% yield from anhydride **5** as a single pure diastereomer (>99.9% de). The absolute stereochemistry and enantiopreference of the reaction was established by X-ray analysis of diacid (3*R*,2′*R*)-**7**.[15]

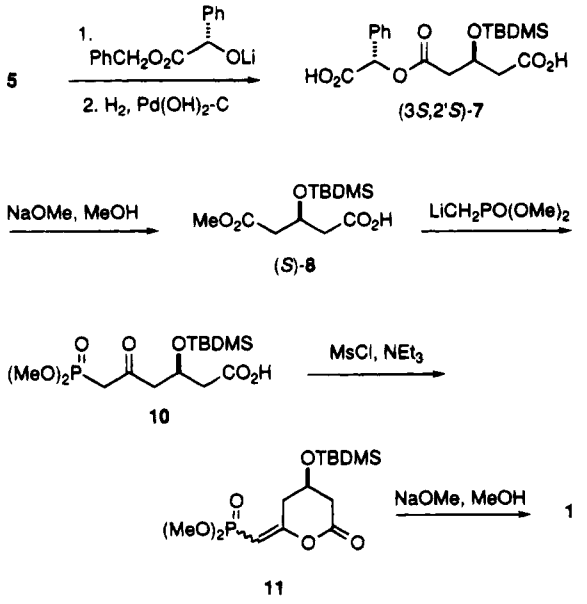
Synthesis of Enantiomerically Pure Monomethyl Ester 8. (*R*)-Monomethyl ester of 3-[(*tert*-butyldimethylsilyl)oxy]pentanedioic acid (*R*)-**8** was prepared from (3*R*,2′*R*)-**7** by a simple ester exchange by treatment with excess of NaOMe in MeOH. After the workup to remove the chiral auxiliary, (*R*)-mandelic acid, monomethyl ester (*R*)-**8** was obtained quantitatively. The enantiomeric excess of (*R*)-**8** was determined to be 99.9% by Heathcock's assay.[4a] This crude acid (*R*)-**8** was sufficiently pure for most purposes including preparation of Wittig reagent **2**, while it was able to be purified by way of its 1-adamantanamine salt.[6]

Our method for the asymmetric synthesis of 3-hydroxyglutaric acid monomethyl ester has two other advantages: one is easy and efficient recovery of a chiral mandelic acid (chiral auxiliary precursor), and the other is high availability of a chiral benzyl mandelate in either enantiomeric form. The chiral mandelic acid was recovered easily by a simple acid treatment, extraction, and subsequent crystallization. Advantage was taken of the availability of the enantiomeric benzyl (*S*)-(+)-mandelate at equal cost, and the same sequence of reaction was repeated by employing the benzyl (*S*)-mandelate as a chiral auxiliary, and dicarboxylic acid (3*S*,2′*S*)-**7** was obtained. The enantiomerically pure monomethyl ester (*S*)-**8** was obtained by the ester exchange (Scheme 4).

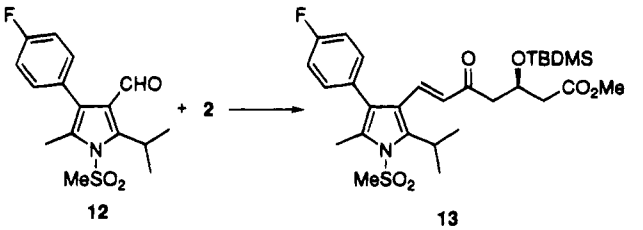
Synthesis of Wittig Reagent 2. Wittig reagent **2** was prepared effectively from the chiral half ester (*R*)-**8** by way of its mixed anhydride **9**. (*R*)-**8** was treated with methyl chlorocarbonate and triethylamine to give the mixed anhydride **9**, and it was subsequently converted to **2** (85% yield from (3*R*,2′*R*)-**7**) by reacting with methylidenetriphenylphosphorane. Wittig reagent **2** is a crystalline compound after chromatographic purification. Wittig reagent **2** showed advantages over HWE reagent **1** in respect that the olefination step is less basic because no additional base is necessary,[16] and it was found useful in the synthesis of HMGR inhibitors having labile functional groups (*vide infra*).[7]

Synthesis of HWE Reagent 1. Previously the 1-adamantanamine salt of chiral monomethyl ester (*S*)-**8** was

Scheme 4



Scheme 5



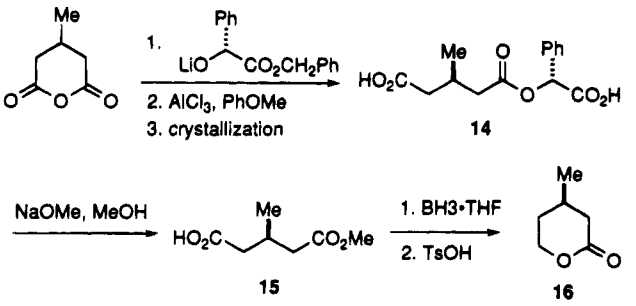
known to be a good precursor for the HWE reagent **1**,[6] therefore, (*S*)-**8** was expected to behave similarly. Treatment of (*S*)-**8** with dimethyl (lithiomethyl)phosphonate (3.5 equiv, THF, −78 °C) followed by diazomethane esterification of the resulting carboxylic acid **10** afforded HWE reagent **1** in 62% overall yield from (*S*)-**8**. However, the use of diazomethane was the drawback for the large scale preparation. To avoid the use of diazomethane, we developed an alternative and safer route. Methyl ester formation from carboxylic acid **10** was accomplished effectively via phosphinyl enol lactone **11** which was obtained by the dehydration (MsCl, NEt_3) of **10**. The phosphinyl enol lactone **11**, consisting of a mixture of *Z*- and *E*-isomers, is a reactive ester and was converted to methyl ester **1** by treatment with methanol and a catalytic amount of sodium methoxide in 55% overall yield from (*S*)-**8**.

These entire sequences for the preparation of **1** and **2** can be carried out without chromatographic purification of the intermediates and require only purification of the final products. The foregoing processes, which utilize readily available optically active benzyl mandelates as chiral sources, are efficient and quite safe and have been used to prepare **1** and **2** in a several 100-g scale. Both reagents reacted with a variety of aldehydes to give high yields of the corresponding enones of *E*-configuration, which are precursors of the 3,5-dihydroxyheptanoic acid moiety found in many HMGR inhibitors. Synthetic utility of Wittig reagent **2** over **1** is shown in the following synthesis of the precursor of the potent HMG-CoA reductase inhibitor (Scheme 5).[7c] Wittig reagent **2** condensed with unstable aldehyde **12** to give enone **13**,[7c] in contrast, **1** did not give **13** under conditions employing several kinds of bases (NaH, LiHMDS, DBU, K_2CO_3,

(15) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(16) Blackwell, C. M.; Davidson, A. H.; Launchburry, S. B.; Lewis, C. N.; Morris, E. M.; Reeve, M. M.; Roffey, J. A. R.; Tipping, A. S.; Todd, R. S. *J. Org. Chem.* **1992**, *57*, 1935.

Scheme 6



Cs_2CO_3) and only extensive cleavage of methanesulfonyl group was observed.

Synthesis of Chiral 3-Methylglutaric Acid, Monomethyl Ester 15. Our strategy for obtaining the chiral half ester was applied to 3-methyl-, 3-phenylglutaric anhydrides, and some other prochiral anhydrides. However, for most of the anhydrides, diastereoselectivity of the ring-opening by chiral benzyl mandelate was not as high as for anhydride **5**. Only 3-methylglutaric anhydride showed moderate selectivity. Scheme 6 shows the synthetic route of (3*R*)-3-methylglutaric acid, monomethyl ester. The reaction of 3-methylglutaric anhydride with lithium salt of benzyl (*R*)-(−)-mandelate in THF at −78 °C gave a 3:1 mixture of diastereomeric acids in quantitative yield. The resulting mixture was treated with $AlCl_3$−anisole[17] which is more satisfactory for deprotection of the benzyl ester than hydrogenolysis. Only benzyl group was deprotected under $AlCl_3$−anisole condition and the mandelate moiety remained intact; however, this condition was not applicable for benzyl ester **6** which has an acid-sensitive silyloxy group. A subsequent crystallization gave the dicarboxylic acid **14** in moderate yield. Recrystallization of **14** gave optically enriched **14** in 35% yield and 99.2% de. The dicarboxylic acid **14** was transformed to the known monomethyl ester **15**[18a] by ester exchange, and its optical purity was determined to be 99.0% ee by HPLC using conditions similar to those reported by Oda.[18c] Monomethyl ester **15** was subsequently converted to (3*R*)-methylvalerolactone **16**[5,18a,19] and identified with the authentic sample, and the absolute configuration was confirmed. Both **15** and **16** are useful chiral building blocks and used in our total synthesis of 3-*epi*-mevinolin, which will be reported.

The relatively low selectivity of the ring-opening of 3-methyl- and 3-phenylglutaric anhydrides is probably due to their flexible conformation in contrast to the conformationally rigid anhydride **5** which has an electron-withdrawing silyloxy group at 3-position and there may be two or more alternative transition state conformations for the ring-opening of these anhydrides bearing electron-releasing groups.

Experimental Section

General. Reactions were carried out under a nitrogen atmosphere in anhydrous solvents (dried over molecular sieves type 4A). Organic extracts were dried over anhydrous $MgSO_4$. Solvent removal was accomplished at aspirator pressure using a rotary evaporator. TLC was performed with Merck precoated TLC plates silica gel 60 F_{254}, and compound visualization was effected with a 10% H_2SO_4 containing 5% ammonium molybdate and 0.2% ceric sulfate. Gravity chromatography was done with Merck silica gel 60 (70−230 mesh). Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were determined as $CDCl_3$ solutions at 200 and 50.3 MHz. *J* values are given in Hz. High-resolution mass spectra (HR-LSIMS) were recorded on a HITACHI M-90 instrument.

3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioic Acid, 1-[Benzyl (*R*)-mandelate] Ester (6a,b). A solution of benzyl (*R*)-mandelate (24.23 g, 0.1 mol) in THF (480 mL) was cooled to −78 °C, and a solution of 1.6 M BuLi in hexane (66 mL, 0.106 mol) was added dropwise, and the mixture was stirred for 20 min. To the reaction mixture was added a solution of 3-[(*tert*-butyldimethylsilyl)oxy]pentanedioic anhydride **5** (24.44 g, 0.1 mol) in THF (100 mL), and the resulting mixture was stirred for 2 h. The reaction mixture was acidified with 2 M HCl and the product was extracted with EtOAc. The organic layer was washed with water and aqueous NaCl and then concentrated to give 48.2 g (99%) of a mixture of diastereomers **6a** and **6b**. The ratio of **6a** and **6b** was determined to be 9:1 by integration of methyne resonances in the ^1H NMR spectrum (**6a**: δ 5.98, **6b:** 5.96). The isomer ratio was further confirmed by HPLC analysis of the debenzylated compounds (see next paragraph of the Experimental Section). **6a**: ^1H NMR: δ 0.03 (s, 3), 0.05 (s, 3), 0.82 (s, 9), 2.61−2.68 (m, 4), 4.53−4.63 (m, 1), 5.10, 5.17 (ABq, 2, *J* = 12.5), 5.98 (s, 1), 7.17−7.48 (m, 10).

(3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioic Acid, 1-[(*R*)-Mandelic Acid] Ester ((3*R*,2′*R*)-7). To the crude extracts of **6a** and **6b** (72.3 g, 0.15 mol) in EtOAc (ca. 1.5 L), was added 1.0 g of Pearlman's catalyst, and the mixture was stirred at room temperature in a hydrogen atmosphere under ordinary pressure until 3.36 L of hydrogen (0.135 mol, 0.93 equiv) was absorbed. The reaction mixture was filtered to remove the catalyst, and the filtrate was extracted with 5% $NaHCO_3$ (600 mL). The organic layer was extracted with additional 5% $NaHCO_3$ (150 mL) and the resulting aqueous layer was washed with EtOAc (300 mL). After the aqueous layer was partitioned with CH_2Cl_2 (500 mL) and acidified with 36% HCl (45 mL), the aqueous layer was extracted with CH_2Cl_2 and the organic layer was washed twice with water. The combined organic extracts were dried and concentrated to give a mixture of diastereomers, and the ratio proved to be 90:10 by HPLC. Crystallization from toluene gave 38 g of (3*R*,2′*R*)-**7** in 98% de. Recrystallization from EtOAc−toluene gave 36.3 g (61% yield) of an enatiomerically pure single diastereomer (3*R*,2′*R*)-**7** (>99.9% de). The de was determined by HPLC [column, Capcell pak C_{18} (AG 120); solvent, MeCN/MeOH/H_2O/AcOH (300/200/350/1); flow rate, 1.0 mL/min; detection, 225 nm; t_R 13.3 min ((3*R*,2′*R*)-**7**), 16.8 min ((3*S*,2′*R*)-**7**)].

(3*R*,2′*R*)-**7**: mp 141−142 °C. IR (KBr): 3700−2400, 1735, 1712, 1253, 1188, 1167, 1080, 980, 832 cm^{-1}. ^1H NMR: δ 0.04 (s, 3), 0.05 (s, 3), 0.82 (s, 9), 2.53−2.84 (m, 4), 4.53−4.66 (m, 1), 5.95 (s, 1), 7.38−7.49 (m, 5). ^{13}C NMR: δ −5.1, −4.9, 17.8, 25.6, 41.9, 42.0, 65.8, 74.2, 127.7, 128.9, 129.5, 132.9, 169.9, 174.5, 177.4. $[\alpha]^{23.5}_D$ −70.2 ± 1.1° ($CHCl_3$, *c* 1.008). Anal. Calcd for $C_{19}H_{28}O_7Si$: C, 57.55; H, 7.12. Found: C, 57.39; H, 7.08.

Hydrogen (3*R*)-1-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate ((*R*)-8). To an ice-cold solution of 28% NaOMe in MeOH (310 mL) was added dropwise a solution of (3*R*, 2′*R*)-**7** (65 g, 0.163 mmol) in MeOH (60 mL) over 45 min keeping the reaction temperature below 7 °C. Stirring was continued for 30 min and the mixture was poured into the mixture of 36% HCl (50 mL), water (300 mL), and CH_2Cl_2 (500 mL). The organic layer was washed with water three times, dried and concentrated to give monomethyl ester (*R*)-**8** (45.07 g, 99%). The enantiomeric excess of (*R*)-**8** was determined by Heathcock's method and proved to be >99.9% ee. (*R*)-**8**: IR (KBr): 2880, 1734, 1712, 1438, 1305, 1096, 836 cm^{-1}. ^1H NMR: δ 0.08 (s, 3), 0.09 (s, 3), 0.86 (s, 9), 2.52−2.73 (m, 4), 3.68 (s, 3), 4.55 (quintet, 1). ^{13}C NMR: δ −4.95, 17.90, 25.63, 42.22, 51.66, 66.10, 171.33, 176.77. $[\alpha]^{23.5}_D$ −5.0 ± 0.4° ($CHCl_3$, *c* 1.04). (*R*)-Mandelic acid was recovered as described below. The aqueous washings were combined and extracted with

(17) Tsuji, T.; Kataoka, T.; Yoshioka, M.; Sendo, Y.; Nishitani, Y.; Hirai, S.; Maeda, T. *Tetrahedron Lett.* **1979**, *20*, 2793.
(18) (a) Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047. (b) Yamamoto, K.; Nishioka, T.; Oda, J.; Yamamoto, Y. *Tetrahedron Lett.* **1988**, *29*, 1717. (c) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc. Perkin. Trans. 1*, **1987**, 1053.
(19) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556.

EtOAc (twice). The organic layer was washed with water and dried and condensed to give crystalline (*R*)-mandelic acid (21 g, 85%).

Mixed Anhydride 9. A solution of (*R*)-**8** (25 g, 91 mmol) and triethylamine (11 g, 109 mmol) in toluene (500 mL) was cooled to −40 °C, and methyl chlorocarbonate (9.4 g, 100 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C and was stirred for 1 h and then poured into water and washed with saturated $NaHCO_3$, and aqueous NaCl. The aqueous washings were extracted with EtOAc and the combined organic fractions were dried and condensed to give 31 g (98% yield) of the anhydride **9** as a clear oil. ^{1}H NMR: δ 0.08 (s, 3), 0.09 (s, 3), 0.86 (s, 9), 2.51−2.86 (m, 4), 3.68 (s, 3), 3.92 (s, 3), 4.55 (quintet, 1, J = 6.0).

Wittig Reagent 2. A suspension of methyltriphenylphosphonium bromide (71 g, 199 mmol) in THF (300 mL) was cooled to −60 °C, and 1.6 M BuLi (120 mL, 192 mmol) in hexane was added dropwise over 20 min. The mixture was allowed to warm to 0 °C. The mixture was cooled to −60 °C, and the toluene solution of the anhydride **9** was added through a cannula over 1 h. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was poured into water and washed with saturated $NaHCO_3$, and aqueous NaCl. The aqueous washings were extracted with EtOAc and the combined organic fractions were dried and condensed. The residual material was purified by silica gel chromatography (hexane/EtOAc = 1/1) to obtain 40.8 g (85%) of Wittig reagent **2**. Recrystallization from Et_2O/hexane gave analytically pure sample. Mp 77.5−78.5 °C. IR (KBr): 2880, 1730, 1528, 1437, 1250, 1106, 835 cm^{-1}. ^{1}H NMR: δ 0.04 (s, 3), 0.06 (s, 3), 0.83 (s, 9), 2.4−2.9 (m, 4), 3.64 (s, 3), 3.74 (d, 1, $^2J_{PH}$ = 26), 4.55 (quintet, 1), 7.4−7.8 (m, 15H). ^{13}C NMR: δ −5.0, −4.4, 17.9, 25.8, 42.5, 49.8 (d, J = 15.1), 51.2, 52.4 (d, J = 106), 68.6, 127.0, (d, J = 90.5), 128.8 (d, J = 12.7), 132.0 (d, J = 2.4), 133.1 (d, J = 10.4), 172.7, 189.8 (d, J = 1.6). $[\alpha]^{22.0}_D$ −6.2° ($CHCl_3$, c 1.27). Anal. Calcd for $C_{31}H_{39}O_4PSi$: C, 69.53; H, 7.35; P, 5.79. Found: C, 69.53; H, 7.35; P, 6.09.

3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioic Acid, 1-[Benzyl (*S*)-mandelate] Ester, (3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioic Acid, 1-[(*S*)-Mandelic Acid] Ester ((3*S*,2′*S*)-7), and Hydrogen (3*S*)-1-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate ((*S*)-8). These title compounds were prepared by a method similar to that for (*R*)-**8** by using benzyl (*S*)-(+)-mandelate (*vide supra*).

(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-(dimethoxyphosphinyl)-5-oxohexanoic Acid, Methyl Ester (1). To a solution of dimethyl methylphosphonate (2.14 g, 17.2 mmol) in THF (20 mL) at −78 °C was added dropwise a solution of 1.6 M BuLi in hexane (10 mL, 16 mmol) over 5 min. After stirring for 30 min, a solution of (*S*)-**8** (1.293 g, 4.68 mmol) in THF (10 mL) was added dropwise. After being stirred for 1.5 h, the reaction mixture was quenched by the dropwise addition of saturated NH_4Cl solution (15 mL) and the mixture was allowed to warm to room temperature. The mixture was acidified with 1 N HCl and extracted with EtOAc. The organic phase was washed with 1 N HCl and saturated NaCl solution, dried, and concentrated to give the crude keto phosphonate acid **10** as a colorless oil (1.69 g, 98%): TLC ($CHCl_3$/MeOH = 10/1) R_f 0.41.

To a solution of crude acid **10** (841 mg) in CH_2Cl_2 (8.5 mL) at −78 °C was added Et_3N (0.792 mL, 5.7 mmol) and MsCl (0.212 mL, 2.74 mmol) dropwise. The mixture was allowed to warm to room temperature and stirred for an additional 30 min. The mixture was poured into 1 N HCl and extracted with CH_2Cl_2. The organic phase was washed with aqueous $NaHCO_3$, dried, and condensed to give enol lactone **11** (659 mg, 82%) that proved to be a 3:1 mixture of double bond isomers by ^{1}H NMR analysis of the olefinic hydrogen peaks (major isomer: δ 4.91, minor isomer: δ 5.25). ^{1}H NMR: δ 0.04 (s, 6), 0.87 (s, 9), 2.5−2.9 (m, 4), 3.76 (d, 3, $^3J_{PH}$ = 11.2), 3.81 (d, 3, $^3J_{PH}$ = 11.2), 4.2−4.4 (m, 1), 4.91 (d, 1, J = 8.9).

A solution of crude enol lactone **11** (659 mg) in MeOH (7 mL) was treated with 1 N NaOMe (0.18 mL) in MeOH at 0 °C for 20 min and quenched with 1 N HCl. The mixture was extracted with CH_2Cl_2 and organic phase was washed with aqueous $NaHCO_3$, dried, and condensed. The crude methyl ester was purified by silica gel chromatography eluting with $CHCl_3$/MeOH (10/1) to give pure **1** (481 mg, 67% (55% yield from (*S*)-**8**)). IR ($CHCl_3$): 2950, 2850, 1729, 1256, 1036, 836 cm^{-1}. ^{1}H NMR: δ 0.06 (s, 3), 0.07 (s, 3), 0.84 (s, 9), 2.4−2.6 (m, 2), 2.88 (d, 2, J = 6.2), 3.11 (d, 2, J = 22.6), 3.67 (s, 3), 3.76 (s, 3), 3.82 (s, 3), 4.47 (quintet, 1, J = 6.0). ^{13}C NMR: δ −5.0, −4.8, 17.9, 25.7, 42.1, 42.4 (d, J = 128), 51.1, 51.6, 53.0 (d, J = 6.4), 53.1 (d, J = 6.4), 65.4, 171.4, 200.0 (d, J = 6.4). $[\alpha]^{22.0}_D$ −0.9 ° ($CHCl_3$, c 1.23). Anal. Calcd for $C_{15}H_{31}O_7PSi$: C, 47.11; H, 8.17; P, 8.10. Found: C, 47.05; H, 7.88; P, 7.86.

Condensation of 1 with Pyrrole Aldehyde 12. A mixture of **2** (17.0 g, 31.8 mmol) and aldehyde **12** (15.41 g, 47.7 mmol) in acetonitrile (170 mL) was refluxed for 24 h. The mixture was condensed and the residue was purified by silica gel chromatography eluting with $CHCl_3$/MeOH (10/1) to give enone **13** (7.48 g, 41%) as clear oil. IR ($CHCl_3$): 2955, 2931, 1734, 1681, 1593, 1371, 1178 cm^{-1}. ^{1}H NMR: δ −0.03 (s, 3), 0.02 (s, 3), 0.80 (s, 9), 1.46 (d, 6, J = 7.5), 2.22 (s, 3), 2.41 (dd, 1, J = 15.0, 6.9), 2.47 (dd, 1, J = 15.0, 6.9), 2.47 (dd, 1, J = 15.6, 6.3), 2.58 (dd, 1, J = 15.6, 6.3), 3.25 (s, 3), 3.65 (s, 3), 3.95 (quintet, 1, J = 7.2), 4.48 (quintet, 1, J = 6.3), 5.53 (d, 1, J = 15.9), 7.0−7.2 (m, 4), 7.73 (d, 1, J = 15.9). ^{13}C NMR: δ −5.0, −4.8, 13.6, 17.9, 23.3, 25.7, 26.5, 42.6, 43.8, 49.1, 51.5, 66.2, 115.7 (J = 22.4), 119.4, 124.65, 126.8, 129.7, 130.4 (J = 4.2), 132.2 (J = 8.5), 134.5, 143.6, 162.4 (J = 247), 171.6, 197.4. $[\alpha]^{23}_D$ +5.9° ($CHCl_3$, c 0.828). Anal. Calcd for $C_{29}H_{42}NO_6SFSi$: C, 60.08; H, 7.30; N, 2.42; F, 3.28. Found: C, 60.44; H, 7.44; N, 2.58; F, 3.34. HR-LSIMS m/z 580.2563 $[M + H]^+$ (calcd for $C_{29}H_{43}NO_6SFSi$, 580.2562).

3-Methylglutaric Acid, 1-[Benzyl (*R*)-mandelate] Ester. A solution of benzyl (*R*)-mandelate (7.27 g, 30 mmol) in THF (100 mL) was cooled to −78 °C, a solution of 1.6 M BuLi in hexane (18.8 mL, 30 mmol) was added dropwise, and the mixture was stirred for 30 min. To the reaction mixture was added a solution of of 3-methylglutaric anhydride (3.84 g, 30 mmol) in 30 mL of THF, and the resulting mixture was stirred for 2 h. The reaction mixture was acidified with 2 N HCl and the product was extracted with EtOAc. The organic layer was washed with water and an aqueous solution of NaCl and then concentrated to give 11.9 g (quantitative) of a mixture of two diastereomers. TLC ($CHCl_3$/MeOH = 10/1) R_f 0.58. ^{1}H NMR: δ 1.05 (d, 3, J = 6.3), 1.6−2.1 (m, 5), 5.05−5.20 (m, 2), 5.95 (s, 1), 7.1−7.5 (m, 10). The ratio of diastereomers was determined to be 3:1 by HPLC after conversion to dicarboxylic acid **13** and the isomer.

(3*R*)-3-Methylglutaric Acid, 1-[(*R*)-Mandelic Acid] Ester (14). To a solution of a mixture of two diastereomeric esters (11.9 g) in anisole (20 mL) and CH_2Cl_2 (100 mL) at −20 °C, was added dropwise a solution of $AlCl_3$ (16 g, 0.12 mol) in nitromethane (60 mL). The mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was cooled at −40 °C, diluted with EtOAc (300 mL), and quenched with 4 N HCl (300 mL). The organic phase was washed with 1 N HCl and partitioned with 5% $NaHCO_3$ (150 mL). The aqueous layer was separated and washed with EtOAc. The aqueous layer was partitioned with EtOAc and acidified with 4 N HCl. The organic layer was washed with water, dried and condensed. The resulting crude dicarboxylic acids were dissolved in EtOAc (20 mL) and toluene (50 mL), and the solution was condensed under reduced pressure to ca. 25 mL to give white crystalline diacid **14** (3.38 g). mp 139−142 °C. The de was determined to be 95% de by HPLC using Capcell pak C_{18} (SG 120). Solvent, Pic A/MeOH (60/40); flow rate 0.8 mL/min; detection 225 nm; t_R 8.9 min (major isomer) and 11.2 min (minor isomer). A single recrystallization from EtOAc/toluene gave 2.98 g (35% yield) of purified diacid. 99.2% de. Mp 143−146 °C. TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.88. $[\alpha]^{23.5}_D$ −105.9 ± 1.4° ($CHCl_3$, c 1.012). IR (KBr): 3600−2400, 1750, 1700, 1428, 1228, 1209, 1160, 1140 cm^{-1}. ^{1}H NMR (d_6-acetone): δ 1.07 (d, 3), 2.2−3.6 (m, 5), 5.93 (s, 1), 7.4−7.6 (m, 5). ^{13}C NMR: δ 19.8, 28.2, 40.6, 40.9, 75.3, 128.9, 129.8, 130.2, 135.8, 170.7, 172.7, 174.3. Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.00; H, 5.75. Found: C, 59.95; H, 5.75.

Hydrogen (3*R*)-1-Methyl 3-Methylglutarate (15). To an ice-cold 28% solution of NaOMe in MeOH (300 mL) was added dropwise a MeOH (85 mL) solution of **14** (43.5 g, 155 mmol)

over 45 min keeping the reaction temperature below 7 °C. Stirring was continued for 20 min and the mixture was poured into the mixture of 36% HCl (150 mL), water (1 L), and CH_2Cl_2 (1 L). The organic layer was washed with water three times, dried, and concentrated to give 20.14 g (81%) of monomethyl ester **15**. IR ($CHCl_3$): 3600–2400, 1723, 1698, 1433cm^{-1}. ^{1}H NMR: δ 1.06 (d, 3, J = 6.6), 2.20–2.55 (m, 5), 3.68 (s, 3). ^{13}C NMR: δ 19.87, 27.21, 40.53, 51.60, 172.84, 178.43. $[\alpha]^{26.0}_{365}$ +1.7 ± 0.3° ($CHCl_3$, c 1.283). Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.19; H, 7.39.

Determination of ee of 14. The enantiomeric excess of **15** was determined by HPLC according to Oda's method by converting **15** to chiral amide and proved to be 99.0% ee and further confirmed after conversion to (3*R*)-3-methylvalerolactone **16**.

To a solution of **15** (18 mg, 0.5 mmol) in CH_2Cl_2 (0.2 mL) was added (*S*)-(−)-α-(1′-naphthyl)ethylamine (0.088 mL, 0.55 mmol) and dicyclohexylcarbodiimide (123 mg, 0.6 mmol). The mixture was stirred for 12 h and the precipitated dicyclohexylurea was removed by filtration. The resulting filtrate was condensed and purified by silica gel chromatography (hexane/EtOAc = 1/1) to give diasteromeric mixture of (3*R*,1′*S*)-3-[methyl-5-(1-naphthyl)ethylamino]-5-oxopentanoic acid, methyl ester and 3*S*,1′*S* isomer. The de was determined to be 99.0% by HPLC [column; Merck Hibar 250-4, solvent; hexane/2-propanol/NEt_3 (15/1/0.16), flow rate; 1.5 mL/min, detection 280 nm, t_R 6.4 min (3*R* isomer), 6.1 min (3*S* isomer). IR ($CHCl_3$): 3424, 3002, 1727, 1659, 1502 cm^{-1}. ^{1}H NMR: δ 0.99 (d, 3, J = 6.6), 1.66 (d, 3, J = 6.2), 1.9–2.6 (m, 5), 3.63 (s, 3), 5.8–6.0 (m, 2), 7.4–7.6 (m, 4), 7.7–7.9 (m, 2), 8.0–8.2 (m, 1). ^{13}C NMR: δ 19.86, 20.62, 28.23, 40.33, 43.04, 44.41, 51.50, 122.55, 123.50, 125.17, 125.88, 126.53, 128.39, 128.75, 131.11, 133.90, 138.19, 170.38, 173.06. $[\alpha]^{24.0}_D$ +25.67° ($CHCl_3$, c 1.27). TLC (EtOAc/hexane = 1/1) R_f 0.52. HR-LSIMS m/z 314.1753 [M + H]$^+$ (calcd for $C_{19}H_{25}NO_3$, 314.1754).

(*R*)-3-Methylvalerolactone (16). To a solution of **15** (7.4 g, 46.2 mmol) was added a 1.0 M THF solution of borane–tetrahydrofuran complex (51.0 mL, 51.0 mmol) dropwise over 10 min at −20 °C. The mixture was warmed up to room temperature and stirred for 3 h. Then ice and H_2O (50 mL) were added followed by K_2CO_3 (12.3 g, 89.0 mmol). The resulting mixture was diluted with EtOAc (100 mL) and the organic layer was separated. The aqueous phase was further extracted with EtOAc (100 mL × 2) and the combined organic layer was dried and concentrated. The residual oil was dissolved in benzene (50 mL) and a catalytic amount of *p*-toluenesulfonic acid (0.30 g) was added. The whole mixture was refluxed azeotropically for 3 h and concentrated. The residue was distilled under reduced pressure (bp. 78–80 °C/4 mmHg) to give **16** (3.08 g, 58%). $[\alpha]^{24.0}_D$ +25.67° ($CHCl_3$, c 1.27) [lit.[19] $[\alpha]^{25}_D$ +27.6° ($CHCl_3$, c 5.6)]. The other spectral characteristics were in agreement with those reported in the literature and the observed specific rotation indicates that the lactone is 93% ee. IR ($CHCl_3$): 2952, 1718, 1397, 1252, 1227 cm^{-1}. ^{1}H NMR: δ 1.07 (d, 3, J = 6.2), 1.4–1.6 (m, 1), 1.8–2.0 (m, 1), 2.0–2.2 (m, 2), 2.6–2.8 (m, 1), 4.27 (ddd, 1, J = 11.4, 3.9, 3.9), 4.43 (ddd, 1, J = 11.4, 3.8, 3.4). ^{13}C NMR: δ 21.52, 26.66, 30.72, 38.32, 68.64, 172.70. TLC (EtOAc/hexane = 1/1) R_f 0.52. HR-LSIMS m/z 115.0758 [M + H]$^+$ (calcd for $C_6H_{11}O_2$, 115.0758).

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