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Microwave-assisted cleavage of Weinreb amide for carboxylate protection in the synthesis of a (*R*)-3-hydroxyalkanoic acid

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Abstract—A versatile route for the modular synthesis of (*R*)-3-hydroxyalkanoic acids, constituents of the naturally biodegradable poly(3-hydroxyalkanoate) polymers, and its application to the synthesis of (*R*)-3-hydroxydecanoic acid is described. Key steps include a microwave-assisted catalytic transfer hydrogenation and a facile microwave-assisted hydrolysis of an *N*-methoxy-*N*-methyl (Weinreb) amide, which enhances the practicality of this protecting group for carboxylic acids.

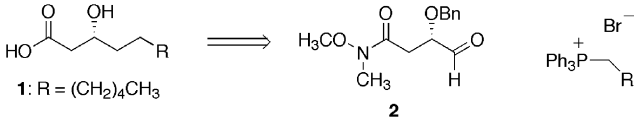
1. Introduction

(*R*)-3-Hydroxyalkanoic acids are common components of lipopeptides, an important class of biologically active compounds that exhibit antimicrobial, insecticidal, and antiviral activities.[1] These acids contain a chiral center and two modifiable functional groups and therefore serve as chiral building blocks for the synthesis of fine chemicals such as antibiotics, vitamins, aromatics, and pheromones.[2] Moreover, (*R*)-3-hydroxyalkanoic acids are constituents of a family of microbial polyesters called poly(hydroxyalkanoates) (PHAs).[3] Although studies of PHAs have been hampered by a limited supply of authentic samples, researchers have nonetheless identified more than 150 different hydroxyalkanoic acids as constituents of these bacterial polyesters.[3c] Herein we report a modular microwave-assisted strategy amenable to the synthesis of (*R*)-3-hydroxyalkanoic acid libraries and its application to the synthesis of (*R*)-3-hydroxydecanoic acid.

Several methods have been reported for the synthesis of optically pure β-hydroxycarboxylic acids including the ruthenium-catalyzed asymmetric hydrogenation of β-ketocarboxylic esters using BINAP ligands,[4] a Grignard reaction for chain elongation of a chiral template,[5] and the use of Evans' chiral auxiliaries when substituents alpha to the carboxylic acid are desired.[6] These procedures suffer the drawbacks of specific substrate requirements for asymmetric induction, limited functional group compatibility, and requirement for chiral auxiliaries, respectively, and hence cannot be used efficiently for the synthesis of libraries of enantiomerically pure (*R*)-3-hydroxyalkanoic acids. To circumvent these liabilities, a commercially available chiral material was chosen as the starting point. The principal disconnection in this strategy is a C–C bond that can be formed by a Wittig reaction; a panel of Wittig salts could be used to obtain a library of (*R*)-3-hydroxyalkanoic acids (Scheme 1). Amide **2** could be made by opening of the (*S*)-3-benzyloxy-γ-butyrolactone with a carboxylate protecting group followed by oxidation of the resulting primary alcohol.

2. Results and discussion

Key to our strategy was the installation of a carboxylic acid protecting group via a simple nucleophilic ring opening of (*S*)-3-hydroxy-γ-butyrolactone. Subsequent deprotection of the acid would require relatively mild conditions since β-elimination of the hydroxyl moiety was a concern. Various nucleophiles such as ethanol, methanol, and benzyl amine have been used for opening



Scheme 1. Retrosynthetic analysis.

Keywords: (*R*)-3-Hydroxyalkanoic acids; Chirality; Weinreb amide; Microwaves; Chiral building blocks; Wittig reaction.
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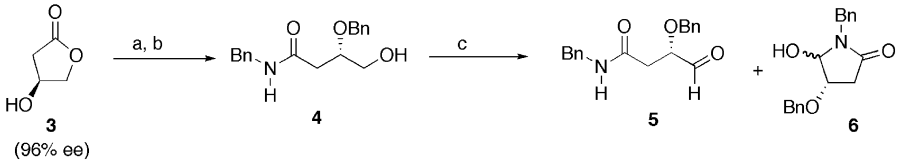
of lactone **3** or its alcohol-protected analog; however, these reactions were low yielding as the alkoxide produced after the opening of the lactone cyclized to return the starting lactone. Amine-based nucleophiles avoid these difficulties. To this end, the benzyl-protected lactone was opened using benzyl amine as the nucleophile with an 80% yield as previously reported.[7] To obtain the aldehyde **5** needed for the Wittig reaction, Parikh and Doering,[8] and Omura and Swern[9] oxidations were explored. As has been observed with previous oxidations of this type, cyclized *N*-acyl hemiaminal **6** (Scheme 2) was isolated as the major product of the reaction; none of the open chain aldehyde form could be trapped in a subsequent Wittig reaction.[8b] Employing a secondary amine would eliminate the potential for cyclization. However, following the protocol described by Weinreb and co-workers[10] with refluxing in dichloroethane at 90 °C for 24 h, 2-oxazolidinone failed to produce the product of lactone opening as evidenced by TLC analysis.

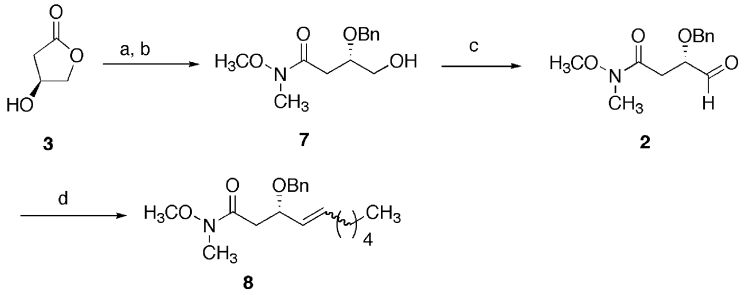
Next, *N*,*O*-dimethylhydroxylamine was considered as the reaction had been previously reported and cleavage of Weinreb amides using anhydrous potassium hydroxide is known.[11] The benzyl-protected lactone ring was opened using *N*,*O*-dimethylhydroxylamine to provide compound **7** in 87% yield (Scheme 3).[12] Subsequent oxidation of the primary alcohol **7** using Parikh–Doering oxidation conditions provided the desired aldehyde **2**. Treatment of this aldehyde with hexyltriphenylphosphonium bromide and KHMDS produced in 86% yield the corresponding Wittig product **8**, which was immediately treated with 10% Pd–C in hydrogen gas atmosphere to obtain compound **9** in 95% yield (Scheme 4).

Because the hydrogenation of **8** required 12 h for completion, a microwave-assisted variant was explored. Catalytic transfer hydrogenation (CTH) has gained attention as a safe and simple hydrogenation technique in which hydrogen gas is replaced with a hydrogen donor such as cyclohexene, hydrazine, or ammonium formate.[13] Recently, microwave-assisted CTH was reported where hydrogenation of the double bond and deprotection of the benzyl group was carried out with 10% Pd–C as a catalyst and ammonium formate as a hydrogen donor in a domestic microwave oven.[13b] Optimal hydrogenation of the Wittig product **8** in a continuous wave microwave reaction vessel was carried out with microwave irradiation at 120 °C using ammonium formate as the hydrogen donor and 10% Pd–C as a catalyst. Critical to the success of the reaction was the addition of ammonium formate after the reaction mixture was brought to 120 °C (Scheme 4). After 5 min of microwave irradiation all of the starting material was consumed and compound **9** was isolated in 90% yield (Scheme 5).

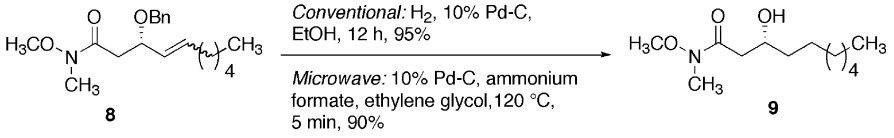
The final challenge was deprotection of the Weinreb amide without elimination of the β-hydroxyl moiety. Weinreb amides are typically hydrolyzed with potassium



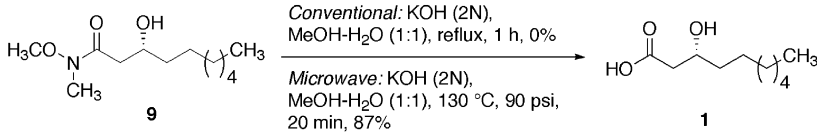
Scheme 2. Reagents and conditions: (a) benzyltrichloroacetimidate, TfOH, CH_2Cl_2–cyclohexane (2:1), 0 °C, 6 h, 71%. (b) benzylamine, benzene, 50 °C, 2 h, 80%. (c) Pyr·SO_3, Et_3N, DMSO, rt, 2 h.



Scheme 3. Reagents and conditions: (a) benzyltrichloroacetimidate, TfOH, CH_2Cl_2–cyclohexane (2:1), 0 °C, 6 h, 71%. (b) (MeO)MeNH·HCl, Me_3Al, CH_2Cl_2, rt, 6 h, 87%. (c) Pyr·SO_3, Et_3N, DMSO, rt, 2 h, 86%. (d) hexyltriphenylphosphonium bromide, KHMDS, toluene, −78 °C, 1 h, 86%.



Scheme 4. Catalytic transfer hydrogenation.



Scheme 5. Microwave-assisted basic hydrolysis of the Weinreb amide.

tert-butoxide (6 equiv) and water (2 equiv) in THF,[11] but these reactions can be difficult. Since aqueous KOH in methanol/water at room temperature has been used to remove the Evans et al. chiral auxiliary,[6] we decided to investigate these conditions to remove the Weinreb amide. The reaction was successful, but took 4 days to go to completion. Recent advances in microwave synthesis[14] inspired us to attempt this hydrolysis under microwave irradiation. Amide **9** was dissolved in MeOH–H_2O (1:1) and subjected to microwave irradiation (130 °C, 90 psi) in the presence of KOH (2 N) (Scheme 3). After 20 min the desired final product **1** was obtained in 87% yield. No product was observed upon conventional heating of the reaction mixture for 1 h. This method delineates a new mild and efficient method to hydrolyze Weinreb amides, thereby rendering this group more practical for the protection of carboxylic acids. This hydrolysis step completed the synthesis (*R*)-3-hydroxydecanoic acid from (*S*)-3-hydroxy-γ-butyrolactone **3**.[15–21]

3. Conclusion

Previous syntheses of chiral β-hydroxy acids have relied on either Grignard reagents for chain elongation and were thereby limited in the functional groups that were tolerated in the side chain or on Evan's chiral auxiliary, which provided mixtures in the absence of an alpha substituent. The use of the versatile Wittig reaction for chain elongation allows the introduction of alkyl groups with varying carbon chain length and different functionalities such as halogen, carboxylic acid, and ester group. These functionalized chiral β-hydroxy acids can be used for the synthesis of a wide variety of complex compounds as well as for the study of the enzyme systems involved in the biosynthesis of poly(hydroxyalkanoates). The dramatic decrease in the observed reaction times for our hydrogenation and Weinreb amide hydrolysis steps further demonstrates the utility of microwave irradiation in synthetic applications.

Acknowledgements

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15. *Analytical data for compound* **7**: (*S*)-3-Benzyloxy-*N*,*O*-dimethyl-4-hydroxybutyramide: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.51 (t, 1H, $J = 6.3$ Hz), 2.61–2.69 (dd, 1H, $J = 6.3$ Hz), 2.83–2.92 (dd, 1H, $J = 5.7$ Hz), 3.18 (s, 3H), 3.58–3.66 (m, 4H), 3.73-3.76 (m, 1H), 4.03–4.07 (m, 1H), 4.57–4.66 (dd, 2H, $J = 11.7$, $J = 3.9$ Hz), 7.23–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 34.4, 41.8, 61.5, 64.2, 72.3, 76.6, 127.9, 128.0, 128.6, 138.6, 172.3; M^+ (EI, 70 eV): 253; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$): +23.1.
16. *Analytical data for compound* **2**: (*S*)-3-Benzyloxy-*N*,*O*-dimethyl-4-oxobutyramide: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.92–2.93 (d, 2H, $J = 4.5$ Hz), 3.19 (s, 3H), 3.67 (s, 3H), 4.27–4.31 (m, 1H),4.67–4.72 (m, 2H), 7.19–7.37

(m, 5H), 9.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 34.4, 41.8, 61.5, 73.5, 79.9, 128.34, 128.36, 128.7, 137.6, 172.3, 202.8; M^+ (EI, 70 eV): 251; $[\alpha]_D^{25}$ (c 1.0, $CHCl_3$): −21.0.

17. *Analytical data for compound* **8**: (*S*)-3-Benzyloxy-*N*,*O*-dimethyldec-4-ene-1-amide: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.88 (t, 3H, $J = 6.6$ Hz), 1.28–1.36 (m, 6H), 2.07–2.12 (m, 2H), 2.44–2.51 (dd, 1H, $J = 5.1$ Hz), 2.89–2.97 (dd, 1H, $J = 8.1$ Hz), 3.16 (s, 3H), 3.64 (s, 3H), 4.39 (d, 1H, $J = 11.7$ Hz), 4.54 (d, 1H, $J = 11.7$ Hz), 4.70–4.78 (m, 3H), 5.35–5.38 (m, 1H), 5.57–5.68 (m, 1H), 7.24–7.31 (m, 5H).
18. *Analytical data for compound* **9**: (*S*)-3-Hydroxy-*N*,*O*-dimethyldecanamide: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.86 (t, 3H, $J = 6.6$ Hz), 1.26–1.56 (br m, 12H), 2.38–2.47 (m, 1H), 2.62 (m, 1H), 3.18 (s, 3H), 3.67 (s, 3H), 3.76 (d, 1H, $J = 2.7$ Hz), 3.96–4.02 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 14.3, 22.8, 25.7, 29.4, 29.7, 32.0, 36.7, 61.4, 68.1, 174.2; M^+ (EI, 70 eV): 231; $[\alpha]_D^{25}$ (c 1.0, $CHCl_3$): −40.0.
19. *Analytical data for compound* **10**: (*S*)-3-Hydroxydecanoic acid: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.87 (t, 3H, $J = 6.8$ Hz), 1.24–1.58 (br m, 12H), 2.43–2.59 (two dd, 2H, $J = 8.8$, $J = 3.2$ Hz), 4.01–4.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.35, 22.89, 25.69, 29.44, 29.48, 32.03, 36.74, 41.26, 68.24, and 177.88; M^+ (EI, 70 eV): 188; $[\alpha]_D^{25}$ (c 1.0, $CHCl_3$): −18.6; 95% ee. Lit. value: −19.7.[22].
20. *Procedure for microwave-assisted hydrogenation*: To a solution of compound **8** (77.0 mg, 0.241 mmol) in ethylene glycol (1 mL) was added 10% Pd–C (23 mg). The reaction mixture was irradiated with microwaves at 10 W in a CEM-Discover continuous wave microwave. The desired temperature of the reaction rose to 120 °C in ~3 min; ammonium formate (152 mg, 2.41 mmol) was then added. The sample was further irradiated with microwaves for a period of 5 min. The solution was poured into water (5 mL) and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated sodium chloride solution (10 mL) and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel column using 40% ethyl acetate/hexane as an eluent. Compound **9** was obtained as an oil (50.0 mg, 0.216 mmol, 90% yield).
21. *Procedure for hydrolysis of Weinreb amide*: Compound **9** (23 mg, 0.121 mmol) was dissolved in 1 mL methanol–water (1:1) and aqueous KOH (2 N, 0.24 mL, 0.48 mmol) was added. The solution was heated at 50 W and 90 psi in a CEM-Discover continuous wave microwave. This pressure was maintained for 20 min during which time the reaction temperature increased from 130 to 136 °C. The irradiation was stopped and the solution was acidified with HCl (2 N, 1 mL). The solution then was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with saturated sodium chloride solution (10 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel column using 60% ethyl acetate/hexane as an eluent. Compound **10** was obtained as white solid (20.0 mg, 0.106 mmol, 87% yield).
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