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Homologation of α-hydroxy acids to α-unsubstituted β-hydroxy carboxamides via Arndt–Eistert reaction

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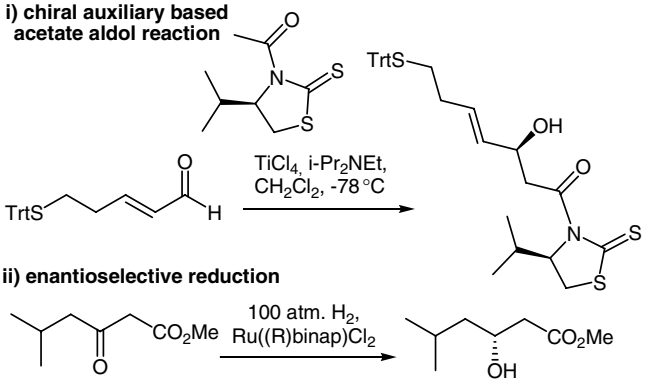
Abstract—Here we studied the homologation of leucic and phenyl lactic acid via Wolff-rearrangement of their diazoketones to the corresponding β-hydroxy acids. This reaction requires distinct conditions to that of their amino acid analogues. The choice of the O^{α}-substituent can selectively direct the reaction to α-unsubstituted β-hydroxy carboxamides or (*E*)-α,β-unsaturated carboxamides and offers a new route from α-hydroxy acids to such compounds.

1. Introduction

Many depsipeptides isolated from marine organisms are attractive targets for medicinal chemistry because of their broad range of biological activities.[1] α-Unsubstituted β-hydroxy carboxylic acids are often present in these architectures and are essential for activity. Synthetic approaches toward these β-hydroxy acids are generally challenging. For example, the α-unsubstituted β-hydroxy carboxylic acid motif of the histone deacetylase inhibitor spiruchostatin A is synthesized via chiral auxiliary-based Aldol reactions with *N*-acetyl thiazolidinethione as an acetate enolate equivalent.[2] This elegant approach provides the enantiopure β-hydroxy acid which is already carboxyl-activated for incorporation into the depsipeptide. The aldehyde required for the Aldol reaction is synthesized from malonic acid monomethylester by a four-step procedure (Scheme 1, i). A second main approach to α-unsubstituted β-hydroxy carboxylic acids is the reduction of the corresponding 3-oxo-carboxylates. For example, 3-hydroxy-5-methyl hexanoic acid ester can be obtained with high enantiomeric purity in quantitative yield by reduction of the corresponding 3-oxo-analogue in the presence of the Noyori catalyst.[3] The 3-oxo carboxylate is prepared from Meldrum's acid and isopentanoyl chloride, the catalyst is generated in situ and the reduction requires 100 atm of hydrogene (Scheme 1, ii). 3-Oxo-carboxylic acids can also be reduced enantioselectively with the chiral borane DIP-Cl[4] and by engineered bacteria.[5]



Scheme 1. Main synthetic pathways to chiral β-hydroxy acids.

In addition to the above mentioned main approaches, alternative and more special routes are already developed, like asymmetric Reformatsky reactions,[6] stereoselective reduction of 1-trimethylsilyl-1-alkyn-3-ones,[7] stereoselective Rh-catalyzed C–H insertion of α-alkoxydiazoketones,[8] enantioselective Al-catalyzed two-step hydration of α,β-unsaturated imides[9] and nucleophilic ring opening of (*S*)-3-hydroxy-γ-butyrolactone with subsequent modification of the terminal hydroxy group.[10]

Keywords: β-Hydroxy carboxylic acids; α,β-Unsaturated carboxylic acids; Microwave shock-heating; α-Hydroxy diazoketones.
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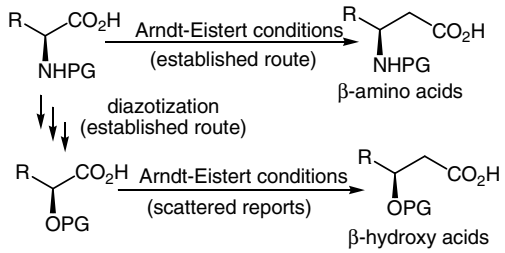


Scheme 2. Homologation of α-hydroxy acids as route to β-hydroxy acids.

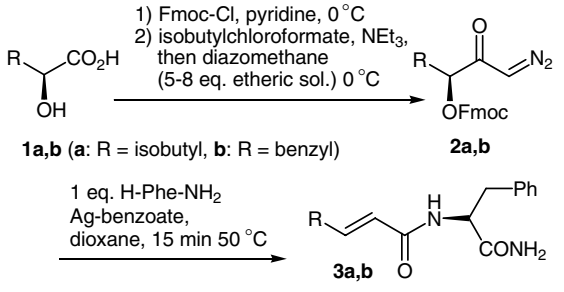
In our current research on depsipeptides, we have found a general access to α-unsubstituted β-hydroxy carboxylic acids bearing the side chains of proteinogenic amino acids a desirable feature. Although, many of the aforementioned protocols are applicable for the enantiopure β-hydroxy-1-carboxylic acid unit, the preparation of the required starting materials, such as the aldehydes for the Aldol-type reactions, or the β-ketoacids for the reductive approach, is often laborious or even not described. On the other hand, it is well known that α-amino acids can be homologized efficiently by the Arndt–Eistert reaction, a synthetic application of the Wolff-rearrangement.[11] We envisioned the Arndt–Eistert homologation of α-hydroxy acids (readily available from α-amino acids by diazotization[12]) as a convenient and general route to the β-hydroxy analogues of interest. This approach would circumvent both the construction of the stereo-centre and the side-chain at the β-carbon because the diazotization and the Arndt–Eistert reaction proceed stereoconservatively under certain conditions. Thus, starting from an amino acid, the corresponding α-unsubstituted β-hydroxy carboxylic acid should be accessible in only four steps: (i) diazotization, (ii) O-protection, (iii) generation of the diazoketone and (iv) Wolff-rearrangement. With respect to the apparent simplicity of this route, only very few applications have been reported. The homologation of all four stereoisomers of *O*-silyl-protected isoleucic acid after O^{α}-deprotection yields 20% of the corresponding β-hydroxy acid methyl esters with (*E*)-α,β-unsaturated carboxylic acid methyl esters as by-products.[13] The homologation of β-amino (or β-azido)-α-hydroxy acids to statins has been reported to produce good (60–71%) yields (Scheme 2).[14]

2. Results and discussion

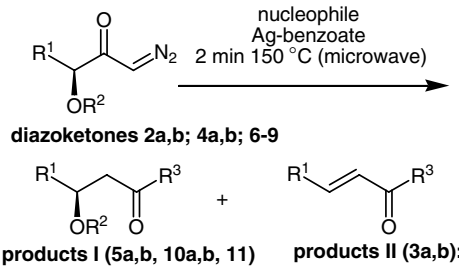
Diazoketones derived from α-amino acids are highly reactive species and undergo Wolff-rearrangement under mild conditions. Thus, Fmoc-homo-β-amino acids are formed from the corresponding diazoketones by ultrasonication in aq dioxane in the presence of Ag^{+} at room temperature.[15] β-Peptides are prepared on solid-phase from diazoketones of α-amino acids and resin-bound amino acids at 0 °C,[16] and β-aminoxy acid amides are obtained from diazoketones of α-aminoxy acids and amines at −78°C.[17] We found diazoketones of α-hydroxy acids to be less reactive. Conversion of Fmoc-OLeu-CHN_2 (**2a**) and Fmoc-OPhe-CHN_2 (**2b**) (obtained in 33% and 39% overall yield from leucic acid (**1a**) and phenyllactic acid (**1b**), respectively, after *O*-Fmoc-protection[18] and carboxyl-activation followed by reaction with etheric solution of diazomethane (Refs. 11b and 15)) required elevated temperatures. On reaction with H–Phe–NH_2 as nucleophile in dioxane at 50 °C for 15 min in the presence of silver benzoate, the homologation/elimination products (*S*)-N^{α}-[(*E*)-5-methyl-hex-2-enoyl]-phenylalanine amide (**3a**, 86%)[19] and (*S*)-N^{α}-[(*E*)-4-phenyl-but-2-enoyl]-phenylalanine amide (**3b**, 72%) were isolated as main products and traces of the homologation products were detected only in the crude reaction mixture. These findings are consistent with other reports on diazoketones bearing an *O*-substituent in α-position (Scheme 3).[20]

The Fmoc-group of **2a** and **2b** were cleaved with 20% piperidine in DMF without affecting the diazoketone moiety, to give the O^{α}-unprotected diazoketones **4a**[21] and **4b**, which have not been described before. Shock-heating was required to induce the reaction of compounds **4**. Microwave irradiation was chosen because it allows controlled heating in small-scale runs.[22] Solutions of **4a** containing equimolar amounts of H–Phe–NH_2 as nucleophile and a catalytic amount of silver benzoate in different solvents were thus reacted for 2 min at 150 °C in a closed microwave reactor. The ^{1}H NMR spectrum of the crude product showed β-hydroxy acid depsipeptide **5a** and the homologation/elimination product **3a**. The ratio of these two products was determined by comparing the ^{1}H NMR integration values for the α-CH_2 of the homologation product **5a** (two dd at 2.25 ppm) and the olefinic proton R–*CH*=CH–CH_2–$CH(CH_3)_2$ of **3a** (m at 5.92 ppm). The ratio was strongly influenced by the solvent used. However, the best yields were obtained in solvent-free reactions. In this case, depsipeptide **5a** was isolated in 47% yield[23] and depsipeptide **5b** from diazoketone **4b** in 48% yield. Prolonging the heating time up to 10 min did not alter the ratio of products, therefore thermal dehydratation of **5a** to **3a** was excluded as a possible origin of olefinic compound (Scheme 4, Table 1).

To find out the most valuable candidates for the Wolff-rearrangement, diazoketones of leucic acid bearing the most common O-protecting groups were synthesized. The *O*-acetyl protected diazoketone **6**[24] was obtained from *O*-acetyl leucic acid. The tetrahydropyranyl (THP)-protected leucic acid (Ref. 18) gave diazoketone



Scheme 3. Homologation/elimination of O^{α}-substituted diazoketones.



Scheme 4. Course of the reaction of diazoketones. Effect of solvent on product ratio: Table 1. Effect of R^2 on product ratio: Table 2. Effect of nucleophile on product ratio: Table 3. **2a** $R^1 = {}^i$Bu, R^2 = Fmoc; **2b** R^1 = Bzl, R^2 = Fmoc; **3a** $R^1 = {}^i$Bu, R^3 = Phe–NH_2; **3b** R^1 = Bzl, R^3 = Phe–NH_2; **4a** $R^1 = {}^i$Bu, R^2 = H; **4b** R^1 = Bzl, R^2 = H; **5a** $R^1 = {}^i$Bu, R^2 = H, R^3 = Phe–NH_2; **5b** R^1 = Bzl, R^2 = H, R^3 = Phe–NH_2; **6** $R^1 = {}^i$Bu, R^2 = Ac; **7** $R^1 = {}^i$Bu, R^2 = THP; **8** $R^1 = {}^i$Bu, R^2 = Bzl; **9** $R^1 = {}^i$Bu, R^2 = TBDMS; **10a** $R^1 = {}^i$Bu, R^2 = H, R^3 = NHCHMePh; **10b** R^1 = Bzl, R^2 = H, R^3 = NHCHMePh; **11** R^1 = Bzl, R^2 = H, R^3 = NHMeOMe.

Table 1. Effect of solvents on the reaction of diazoketones **4** with H–Phe–NH_2 (Scheme 4)

Educt	Solvent, time (min)	Ratio **I** (**5**):**II** (**3**)[a]
4a	DMF, 2	Ca. 1:3
4a	DMF, 10	Ca. 1:3
4a	MeOH, 2	Ca. 3:4
4a	MeOH, 10	Ca. 3:4
4a	EtOH, 2	Ca. 1:1
4a	No solvent, 2	Ca. 4:1
4b	No solvent, 2	Ca. 4:1

[a] Determined by ^{1}H NMR integration.

7. The α-OH of leucic acid methylester[25] was benzyl[26] (Bzl)-*tert*-butyldimethylsilyl (TBDMS)- (Ref. 3) protected. Saponification of the methyl ester, followed by activation and reaction of the 1-carboxylic group with diazomethane gave diazoketones **8** and **9**, respectively. When the THP-, Bzl- and TBDMS-ethers (**7**, **8** and **9**, respectively) were reacted with H–Phe–NH_2 following the microwave protocol described above, the homologation and homologation/elimination products were found in a ratio of ca. 1:1. The *O*-acyl-protected diazoketones **2** and **6** gave almost exclusively homologation/elimination products. However, the unprotected diazoketone **4a** still produced the best yields of β-depsipeptide **5**. These findings indicate that protection of the O^{α}-function enhances its tendency to act as leaving group (Scheme 4, Table 2).

We next studied the effect of the nucleophile on the reaction. Diazoketones **4a**,**b** were reacted with different amines and alcohols under the above described conditions. L-α-Methyl benzylamine react with **4a** and **4b** to β-hydroxy carboxamides **10a** and **10b**, which were isolated in 88% and 50% yield, respectively. Reaction of **4a**,**b** with phenylalanine amide yielded depsipeptides **5a** and **5b** in 47% and 48%, respectively. Upon reaction of **4b** with *N*,*N*-methoxy-methylamine, the Weinreb-amide **11** (47%) was obtained. Homologation/elimination was favoured when weaker nucleophiles, such as water, allyl alcohol and also solid phase-bound amino

Table 2. Effect of the O-protecting group of diazoketones on reaction with H–Phe–NH_2 as the nucleophile (Scheme 4)

R^2 of diazoketone ($R^1 = {}^i$Bu)	Ratio **I**/**II** (**3a**)[a]
H (**4a**)	Ca. 4:1
Bzl (**8**)	Ca. 0.8:1
TBDMS (**9**)	Ca. 0.7:1
THP (**7**)	Ca. 0.7:1
Ac (**6**)	Traces of depsipeptide
Fmoc (**2a**)	Traces of depsipeptide

[a] Determined by ^{1}H NMR as described above.

Table 3. Effect of the nucleophiles on the ratios of β-hydroxy acid derivative I/dehydratation product II (Scheme 4)

Diazoketone and nucleophile	Ratio **I**/**II**[a]
4a, 1 equiv L-α-methyl benzylamine	Ca. 6:1 (**10a**, 88%)
4b, 1 equiv L-α–methyl benzylamine	Ca. 7:1 (**10b**, 50%)
4a, 1 equiv H–Phe–NH_2	Ca. 4:1 (**5a**, 47%)
4b, 1 equiv H–Phe–NH_2	Ca. 4:1 (**5b**, 48%)
4b, 3 equiv *N*,*N*-methoxy methylamine	Ca. 3:1 (**11**, 47%)
4a, aq dioxane	Ca. 2.3:1
4a, excess allyl alcohol	Ca. 0.7:1
4a, H–Phe–MBHA rink amide, aq dioxane	Ca. 0.6:1

[a] Determined by ^{1}H NMR in the reaction mixture. The isolated yields of products are shown in parenthesis.

acids, were used. Addition of nucleophile excess did not improve the yields of homologation products (Scheme 4, Table 3). However, this new variant of the Arndt–Eistert reaction required strong heating with amines. To detect racemization, D-leucine was converted into diazoketone **4a**–**D** and reacted with L-α-methylbenzylamine to form the diastereomer **10a**–**D**. Normal phase HPLC of the product revealed a *d.e.* of 86%.

3. Conclusion

To the best of our knowledge, this is the first detailed study of the potential of α-hydroxy acids to undergo Arndt–Eistert homologation via Wolff-rearrangement of their diazoketones. In summary, we have found for α-hydroxy acids a distinct reaction behaviour than that of their amino acid analogues. The tendency of α-hydroxy acids to undergo homologation or homologation/elimination reaction under the applied conditions is a function of the O-substituent, the solvent and the nucleophile. O^{α}-acyl derivates yielded (*E*)-α,β-unsaturated carboxamides (72–86%). O^{α}-Unprotected diazoketones, a so far unknown subclass of diazoketones, favoured homologation to α-unsubstituted β-hydroxy carboxamides (47%–88% isolated yields) on reaction with amines in the presence of catalytic amounts of silver benzoate when shock-heated with microwave irradiation (150 °C, 2 min). Although the scope of this protocol is limited to the use of amines as nucleophilic trapping reagents and partial racemization was detected, it may be useful for the incorporation of β-hydroxy acids in the N-terminal position of peptides and preparation of β-hydroxy carboxamides.

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19. (*S*)-N^{α}-[(*E*)-*5-Methyl-hex-2-enoyl*]-*phenylalanine amide,* **3a**: Diazoketone **2a** (117 mg, 0.31 mmol) and H–Phe–NH_2 (51 mg, 0.31 mmol) were dissolved in dioxane (10 mL). Silver benzoate (7 mg) was added (the solution immediately became brown) and it was heated to 50 °C. After consumption of **2a** (TLC), it was filtered, lyophilized and purified by flash chromatography to give **3a** (73 mg, 86%) as a white solid. $R_f = 0.5$ (AcOEt). Mp 179–181 °C. ^{1}H NMR (CD_3OD): $\delta = 0.91$ (3H, d, $J = 6.66$ Hz), 0.92 (3H, d, $J = 6.67$ Hz), 1.72 (1H, m), 2.06 (2H, m), 2.91 (1H, m), 3.16 (1H, m), 4.68 (1H, m), 5.92 (1H, dt, $J = 15.35$ Hz, $J = 1.3$ Hz), 6.71 (1H, m), 7.17–7.28 (5H, m) ppm. ^{13}C NMR (CD_3OD): $\delta = 22.7$, 22.7, 29.2, 39.1, 42.4, 55.8, 125.4, 127.7, 129.4, 130.3, 138.6, 145.2, 168.3, 176.3 ppm. IR (KBr): $\nu = 3364$, 3283, 2952, 1677, 1612 cm^{-1}. HRMS: Calcd for $C_{16}H_{22}N_2O_2$+Na: 297.1579. Found: 297.1581 $[M+Na]^+$.
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21. (*S*)-*1-Diazo-3-hydroxy-5-methylhexan-2-one (H-OLeu-CHN$_2$)* **4a**: Fmoc-OLeu-CHN_2 **2a** (3.11 g, 8.2 mmol) was dissolved in 20% piperidine in DMF (30 mL) and stirred for 15 min. Volatiles were evaporated under high vacuum and the residue was purified by flash chromatography to give **4a** as a yellow oil (1.1 g, 85%). On prolonged standing at room temperature (several days), the oil decomposes (the colour turns to brown). $R_f = 0.5$ (1 hexane/1 ethyl acetate). ^{1}H NMR ($CDCl_3$): $\delta = 0.96$ (6H, m), 1.46 (2H, m), 1.90 (1H, m), 4.10 (1H, m), 5.52 (1H, br s). ^{13}C NMR ($CDCl_3$): $\delta = 21.3$, 23.3, 24.3, 43.8, 52.7, 73.8, 198.3. IR (film): $\nu = 3421$, 2958, 2108, 1624, 1349 cm^{-1}. **4a**: $[\alpha]_D^{25}$ −95.6 (*c* 3.57, MeOH). The synthesis of **4a**–**D** from D-leucine proceeds analogously. **4a**–**D**: $[\alpha]_D^{25}$ +97.5 (*c* 3.42, MeOH). HRMS: Calcd for $C_7H_{12}N_2O_2$+Na: 179.0797. Found: 179.0795 $[M+Na]^+$.
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23. (*S*)-N^{α}-[(*3S*)-*3-Hydroxy-5-methyl-hexanoyl*]-*phenylalanine amide,* **5a**: Diazoketone **4a** (60 mg, 0.38 mmol) was placed with H–Phe–NH_2 (63 mg, 0.38 mmol) at the bottom of a microwave reactor tube. A catalytic quantity of silver benzoate was added (ca. 7 mg). **Caution**: After addition of silver benzoate to the reaction mixture an exothermic reaction starts with evolution of gas. It origin is not clear, because the ^{1}H NMR spectrum shows an unaltered mixture of starting materials. The tube was sealed, placed in the microwave oven and heated for 2 min to 150 °C (ramp time: 2 min, hold time: 2 min) with 150 W. After reaction, the product was purified by flash chromatography to give **5a** (52 mg, 47%) as a white solid. $R_f = 0.28$ (9 $CHCl_3$/1 MeOH). Mp 158–162 °C. ^{1}H NMR (CD_3OD): $\delta = 0.87$ (6H, m), 1.07 (1H, m), 1.32 (1H, m), 1.72 (1H, m), 2.22 (1H, dd, $J = 14.0$ Hz, $J = 5.2$ Hz), 2.27 (1H, dd, $J = 13.9$ Hz, $J = 7.9$ Hz), 2.86 (1H, dd, $J = 14.0$ Hz, $J = 9.8$ Hz), 3.22 (1H, dd, $J = 14.0$ Hz, $J = 4.9$ Hz), 3.96 (1H, m), 4.66 (1H, m), 7.17–7.30 (5H, m) ppm. ^{13}C NMR (CD_3OD): $\delta = 22.3$, 23.8, 25.5, 38.7, 45.2, 47.5, 55.7, 68.1, 127.8, 129.5, 130.2, 138.7, 174.3, 176.5 ppm. IR(KBr): $\nu = 3398$, 3299, 2954, 1638, 1539 cm^{-1}. HRMS Calcd for $C_{16}H_{24}N_2O_3$+Na: 315.1685. Found: 315.1668 $[M+Na]^+$.
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