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Application of the Schöpf Method to Optimization of the Synthesis of 3-[2-(*p*-*N*-Acetylaminophenyl)ethyl]-3-hydroxy-4-methylpentanoic Acid: Simultaneous Reduction of Three Functional Groups to Maximize Yield and Throughput

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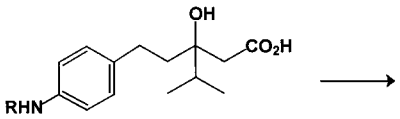
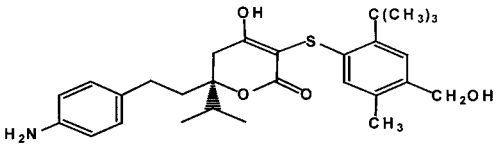
Abstract:

Application of the Schöpf method to development of a high yield condensation process to prepare a labile *β*-(*p*-nitrophenyl)-α,*β*-unsaturated ketone system, along with development of a procedure for simultaneous hydrogenation/hydrogenolysis of olefin, benzyl ester, and nitro groups, allows the construction of an inexpensive route to 3-[2-(*p*-*N*-acetylaminophenyl)ethyl]-3-hydroxy-4-methylpentanoic acid, a key intermediate in the preparation of CI-1029 and related HIV protease inhibitors.

3-Arylthio-4-hydroxy-5,6-dihydropyrones such as CI-1029 are members of a new class of HIV protease inhibitors which are nonpeptidic, competitive, reversible inhibitors of the protease enzyme.[1,2] The 3-arylthio-4-hydroxy-5,6-dihydropyrones enjoy low cross resistance relative to currently marketed peptidomimetic protease inhibitors.[1] Key synthetic intermediates required for the preparation of CI-1029 and related members in this class are the 3-[2-(*p*-N-protected aminophenyl)ethyl]-3-hydroxy-4-methylpentanoic acids (**1**).[2,3] To find a scaleable, cost-effective method for CI-1029, we have developed a high-yield, high-throughput process for **1a** (R = acetyl) which uses inexpensive, readily available raw materials and standard production equipment.



1a: R=Ac



CI-1029

The starting point for the formation of **1** would appear to be a 4-methyl-1-(para-substituted-phenyl)-3-pentanone derivative in which the para substituent may be either a protected (e.g. acylated) amino function or a nitro group. As we shall see below, the nitro group has an advantage over an acylated amino function, particularly when trying to carry out the carbanion chemistry to generate the tertiary alcohol group in **1**. Various types of 4-methyl-1-(para-substituted-phenyl)-3-pentanone derivatives were considered as targets including 1-hydroxy-4-methyl-1-(*p*-nitrophenyl)-pentan-3-one (**4**) and 4-methyl-1-(*p*-nitrophenyl)-1-penten-3-one (**9**). The latter compound has been prepared previously using a rather expensive arsonium Wittig approach[4] or alternatively, from methyl isopropyl ketone and *p*-nitrobenzaldehyde in low overall yield (34%) using a two-step process involving initial base-induced aldol condensation to form *β*-hydroxyketone **4** followed by acid-induced elimination to give **9** which then required column chromatography for purification.[5]

One would expect that a condensation reaction between *p*-nitrob**e**nzaldehyde and methyl isopropyl ketone would be straightforward. However, low yields were encountered when we tried to carry out this reaction under a variety of conditions.[6] Typically, under basic conditions, the reaction would turn black. Complex mixtures were invariably obtained. The solution to this problem became apparent from work reported by Grayson and Tuite[7] who applied the Schöpf[8] method to preparation of certain *β*-hydroxy ketones including a compound, 1-hydroxy-1-(*p*-nitrophenyl)pentan-3-one, that was structurally closely related to the *β*-hydroxyketone **4** that we required. They found that 1-hydroxy-1-(*p*-nitrophenyl)pentan-3-one could be obtained in good yield from *p*-nitrobenzaldehyde and *β*-ketovaleric acid using pyridine as catalyst. The isobutyrylacetic acid (**3**) required

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(5) Barker, S. D.; Norris, R. K. *Aust. J. Chem.* **1983**, *36*, 527.

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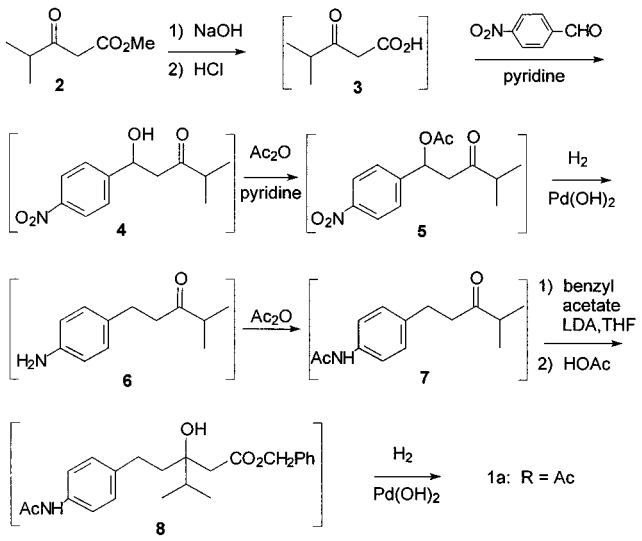
in our case is unstable, readily undergoing decarboxylation at room temperature. Isobutyrylacetic acid was generated in situ by saponification of inexpensive[9] methyl isobutyryl acetate (**2**), followed by acidification with HCl at low temperature (<10 °C). The β-keto acid was then used directly in the next step reacting with *p*-nitrobenzaldehyde to give **4** in high yield. By stopping at **4**, we avoid generation of the labile β-(*p*-nitrophenyl)-α,β-unsaturated ketone system under the strongly basic conditions normally required to bring about the direct condensation of *p*-nitrobenzaldehyde with methyl isopropyl ketone.

With an inexpensive source of **4** now available, we investigated hydrogenation of this system with the hope of achieving simultaneous reduction of both the nitro and benzyl alcohol functions. The yield in this reduction proved mediocre at best due to over reduction of the ketone to produce, as by-product, 1-(*p*-aminophenyl)-4-methyl-3-pentanol. Hydrogenation conditions were varied, but without success in avoiding this side reaction. Further study showed that reduction of the ketone function could be largely avoided by first converting the benzylic alcohol group to its acetate derivative, 1-acetoxy-4-methyl-1-(*p*-nitrophenyl)pentan-3-one (**5**), using acetic anhydride and pyridine as base. For economy purposes, to complete the acetylation, we used the same pyridine employed in the initial Schöpf condensation reaction. Reduction of **5** then proceeded smoothly using 20% palladium hydroxide on carbon to produce 1-(*p*-aminophenyl)-4-methylpentan-3-one (**6**) in high yield. The latter was not isolated but treated directly with acetic anhydride to give the corresponding acetamide derivative, 1-(*p*-*N*-acetylaminophenyl)-4-methylpentan-3-one (**7**). The preparation of **7** in four steps from *p*-nitrobenzaldehyde went sufficiently well to allow us to avoid isolation/purification of **7**. Crude **7** was typically better than 90 area % pure by HPLC analysis in both lab and pilot plant runs. The latter was used directly in the next step in a reaction carried out with excess lithium enolate of benzyl acetate generated in situ from lithium diisopropylamide and benzyl acetate. The resulting tertiary alcohol, 3-[2-(*p*-*N*-acetylaminophenyl)-ethyl]-3-hydroxy-4-methylpentanoic acid benzyl ester (**8**) was also not purified, but instead converted directly into the desired final product, **1a**, by hydrogenolysis over 20% palladium hydroxide catalyst. Overall yields of 65−70% were obtained for the seven-step process (Scheme 1).

This initial method for **1a** was run several times on pilot scale and proved effective in preparation of toxicology and phase I clinical supplies. However, one step in the procedure suffered from poor throughput. In particular the benzyl acetate lithium enolate addition reaction with 1-(*p*-*N*-acetylaminophenyl)-4-methylpentan-3-one (**7**) required more than 3 equiv of the enolate anion for optimum yield. The product of this addition reaction was a bis anion in which the tertiary alcohol function as well as the acetamide group were both ionized. This bis anion had poor solubility in THF and excess solvent was required to maintain agitation.

(9) Several suppliers are available including Wacker Chemicals, Burghausen, Germany, and UBE Industries Inc., Tokyo, Japan.

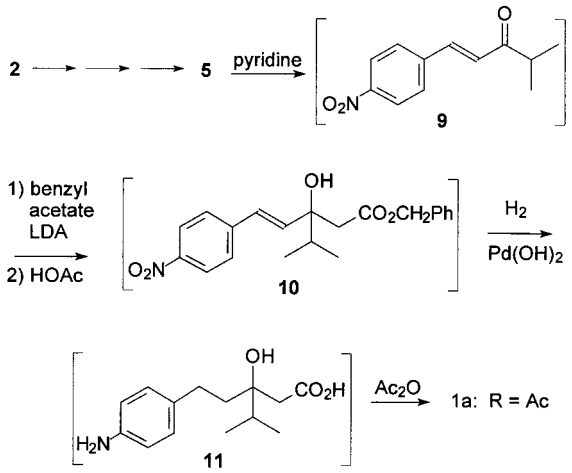
Scheme 1



To address the throughput problem, we considered strategies which would allow us to complete the enolate anion addition procedure in the presence of an amino protecting group that did not contain an acidic proton. The acetamide as well as other well-known acylated derivatives such as BOC- or Z-protected amines were not expected to work well for the purpose of optimizing throughput. Bis acylated amines—for example, phthalimide derivatives—were likely to be too labile in the presence of the strong benzyl acetate enolate anion nucleophile. This led us to consider the nitro group as a protected amine function for the purpose of completing this enolate anion addition step under high throughput conditions. We were not initially encouraged to try this due to our extensive experience with black, complex reaction mixtures whenever we placed a β-(*p*-nitrophenyl)-α,β-unsaturated ketone system in a strongly basic reaction medium. We considered that we may possibly avoid this decomposition process if we take advantage of the fact that enolate carbanion additions to ketones can be carried out at very low temperatures, for example, −70 to −80 °C. The black, polymeric mixtures that we encountered with β-(*p*-nitrophenyl)-α,β-unsaturated ketone intermediates in the presence of strong base, were all seen at relatively high temperature (0−25 °C) or conditions which are typical of most Knoevenagel and Claisen Schmidt condensation reactions. Thus, we tried the addition of the benzyl acetate enolate anion to (*E*)-4-methyl-1-(*p*-nitrophenyl)-1-penten-3-one (**9**) at −60 to −75 °C in THF. Although we did observe the black color, the reaction was clean and produced a high yield of the desired addition product, 3-hydroxy-3-isopropyl-5-(*p*-nitrophenyl)-4-pentenoic acid benzyl ester (**10**). The dark color was reduced by a subsequent carbon treatment.

In addition to helping throughput, this procedure also allowed us to combine the two hydrogenation reactions in our first method. Thus, with 20% palladium hydroxide on carbon as catalyst, we could reduce three functional groups in **10** in one step. This reduction chemistry proceeded cleanly, in high yield and with good throughput. In the development

Scheme 2



of an efficient synthesis of the drug encainide,[10] a different mix of three functional groups, including a nitro group, were also reduced together successfully. The reduction product, **11**, was not isolated but instead treated directly with acetic anhydride to give the desired final product, **1a**. The required intermediate **9** is readily available by warming **5** with the weak base, pyridine. Again for economy, the same pyridine is used that was employed for the initial Schöpf reaction to make **4**. In pilot plant runs the HPLC purity of crude **9** was typically better than 97 area %, and yields of **9** from *p*-nitrobenzaldehyde were estimated to be better than 90%. The overall yield for the seven-step process to produce **1a** from *p*-nitrobenzaldehyde was again in the 65−70% range, producing material which had HPLC purity in excess of 99 area % (Scheme 2).

The only significant impurity found in the process is that formed in the acetylation reaction to produce **11** from **10**. In this conversion we found 10−20% 3-acetoxy-3-[2-(*p*-acetylaminophenyl)ethyl]-4-methylpentanoic acid (**12**) resulting from over acetylation of **11**, probably via the mixed anhydride of **12** with acetic acid. The structure of this impurity was confirmed by independent synthesis. However, **12** could be converted back to **1a** prior to isolation by heating under basic conditions for several hours at 60−75 °C.

In summary, we have developed an economical, high throughput method for preparation of 3-[2-(*p*-*N*-acetylaminophenyl)ethyl]-3-hydroxy-4-methylpentanoic acid (**1a**) in seven combined steps. The method provides product in high purity and is suitable for use in manufacture of the protease inhibitor, CI-1029.

Experimental Section

Melting points were obtained using a Büchi B-545 melting point apparatus. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 200 MHz on a Varian XL 200 NMR spectrometer. Chemical shifts are reported downfield in ppm from an internal tetramethylsilane standard. Analytical high-performance liquid chromatography (HPLC) was carried out using a Hitachi model L-6200 pump, a Hitachi model L-7400 variable wavelength UV detector set at 254 nm. A 4.6 mm × 25 cm 5μ C18 (YMC-AQ) column was used with mobile phases consisting of A: CH_3CN and B: 0.2% aqueous acetic acid in a gradient mode at a flow rate of 1.0 mL/min.

3-[2-(*p*-*N*-Acetylaminophenyl)ethyl]-3-hydroxy-4-methylpentanoic Acid (1a); High-Throughput Process. Methyl isobutyryl acetate (80.0 kg), methyl *tert*-butyl ether (20 L) and water (120 L) were charged to a still under an inert atmosphere, and the mixture was stirred and cooled to 18 °C. Sodium hydroxide (120 kg of a 50% aqueous solution) was added over 80 min while maintaining the temperature between 15 and 23 °C. The mixture was stirred overnight at 24−26 °C and then cooled to 0 °C. Hydrochloric acid (148 kg of a 37% aqueous solution) was added while maintaining the temperature below 5 °C to adjust the pH to 0.1. After settling the aqueous layer was separated and treated with sodium chloride (6 kg) and extracted with methyl *tert*-butyl ether (10 L). The combined organic layers were added to a mixture of *p*-nitrobenzaldehyde (52.0 kg, 344 mmol) and pyridine (102 kg) over 45 min while maintaining the temperature between −2 and −5 °C. The resulting mixture was stirred over the weekend at −2 to 1 °C and then warmed to 32−38 °C where it was held for 5 h. Toluene (60 L) was charged to the mixture which was then cooled to 15 °C and extracted with a solution of sodium carbonate (6 kg) in water (60 L) followed by a solution of sodium chloride (24 kg) in water (60 L). The remaining organic layer was dried over sodium carbonate (20 kg). After filtration to remove the sodium carbonate, the carbonate was washed with toluene (120 L) and the wash combined with the filtrate to provide a solution of 1-hydroxy-4-methyl-1-(*p*-nitrophenyl)pentan-3-one (**4**) in toluene, pyridine, and methyl *tert*-butyl ether. This was cooled to −2 °C and acetic anhydride (68.0 kg) added over 30 min while maintaining the temperature between 0 and −2 °C. The resulting mixture was stirred overnight while maintaining the temperature between 1 and −2 °C, thus providing a solution of 1-acetoxy-4-methyl-1-(*p*-nitrophenyl)pentan-3-one (**5**) in toluene, methyl *tert*-butyl ether, and pyridine. This was heated to 85−87 °C where it was held for 6 h. After cooling to 9 °C, water (80 L) was added with stirring. After settling, the aqueous layer was separated and the organic layer extracted with a solution 37% hydrochloric acid (78 kg) in water (150 L) while including a 10 L toluene rinse to aid in transfer of the organic solution of the product. The latter was treated with 37% hydrochloric acid (26 kg), water (110 L), ADP carbon (4 kg), Supercel Hyflo (12 kg), and toluene (20 L). After stirring the mixture was filtered and the residue rinsed with toluene (60 L). The combined filtrate and rinse were allowed to settle, and the aqueous layer was separated from the organic layer. The latter was extracted with water (50 L). The water extracts were discarded, and the organic solution was concentrated under vacuum to remove solvent. This provides (*E*)-4-methyl-1-(*p*-nitrophenyl)-1-penten-3-one (**9**) as a solid. The **9** was dissolved in tetrahydrofuran (140 L). A solution of the lithium enolate anion of benzyl acetate was prepared starting with 43.0 kg diisopropylamine in 180 L THF followed by treatment of this solution with 30.8 kg 10 M

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n-butyllithium in hexanes at −25 to −58 °C followed by addition of 57.6 kg benzyl acetate to the resulting solution of lithiun diisopropylamide at −59 to −65 °C. The solution of **10** in THF was added to this benzyl acetate enolate anion solution over 2.5 h while maintaining the temperature between −60 to −64 °C. The mixture was stirred another 20 min at −60 to −64 °C and acetic acid (38 kg) was added while maintaining the temperature between −55 to −64 °C. Methanol (120 L) was added, and the mixture was stirred and warmed to 28 °C. Agitation was stopped, and salts were allowed to settle to the bottom of the still. The supernatant was transferred into a second reactor containing ADP carbon (6 kg) and Supercel Hyflo (5 kg). The remaining salts were treated with water (400 L) and toluene (60 L). The aqueous layer was separated and discarded. The upper toluene layer was combined with the supernatant, ADP carbon, and Supercel in the second reactor and the resulting mixture stirred at 20−30 °C for 30 min. This mixture was then concentrated under vacuum to a volume of 520−540 L. The mixture was filtered and the residue washed with a mixture of THF (60 L) and methanol (60 L). The combined filtrates containing 3-hydroxy-3-isopropyl-5-(*p*-nitrophenyl)-4-pentenoic acid benzyl ester (**10**) in methanol−THF solvent were hydrogenated over 11 kg 20% palladium hydroxide catalyst, 50% water wet, at 28−38 °C and 50 psi hydrogen. The hydrogenation mixture was filtered to remove catalyst and the catalyst washed with methanol (80 L) and this combined with the whole to give a solution of 3-[2-(*p*-aminophenyl)-ethyl]-3-hydroxy-4-methylpentanoic acid (**11**) in THF and methanol. The latter was cooled to 4 °C and acetic anhydride (50.0 kg) added over 35 min while maintaining the temperature below 13 °C. The resulting solution was stirred 40 min at 13−15 °C and then concentrated under vacuum to remove solvent and the residue treated with toluene (40 L), methyl *tert*-butyl ether (20 L) and water (300 L). Sodium hydroxide 50% aqueous solution (64 kg) was added to adjust the pH to 12.5 while maintaining the temperature below 22 °C. The resulting mixture was heated to 60−72 °C where it was held overnight. The mixture was cooled to 25 °C, and the layers were separated, and the organic layer was extracted with water (40 L). The organic layer was discarded and the water extract combined with the aqueous product solution. The combined aqueous layers were treated with ethyl acetate (180 L), and 37% hydrochloric acid (109 kg) was added to bring the pH to 2.7 while maintaining the temperature below 15 °C. The aqueous layer was separated and extracted with ethyl acetate (140 L) and the aqueous solution discarded. The combined ethyl acetate extracts were washed twice with a solution of 6 kg 37% hydrochloric acid in 60 L water followed by 60 L water and then concentrated under vacuum to a volume of 100−140 L. Toluene (160 L) was charged to the still and the vacuum distillation continued to reduce the volume again to 100−140 L. Ethyl acetate (60 L) was added to the mixture, which was stirred and cooled to 4 °C and filtered. The solid was washed with ethyl acetate (80 kg and 60 kg) and vacuum-dried at 40 °C until the LOD was less than 0.5%. This provides 64.9 kg (221 mol, 64.3%) of 3-[2-(*p*-*N*-acetylaminophenyl)ethyl]-3-hydroxy-4-methylpentanoic acid (**1a**): mp 157−160 °C; ^{1}H NMR (DMSO-d_6) δ 0.86 (d, 6H), 1,6−1.9 (m, 3H), 1.99 (s, 3H), 2.3−2.6 (m, 5H), 7.07 (d, 2H), 7.44 (d, 2H), 9.81 (s, 1H); HPLC: 99.6 area %; ROI 0.10%. A second crop was isolated from the mother liquors: 4.9 kg (17 mol, 4.9%); mp 147−148 °C; HPLC 95.5 area %. An analytical sample was prepared by recrystallization from ethyl acetate. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.72, H, 7.92; N, 4.65.

1-Hydroxy-4-methyl-1-(*p*-nitrophenyl)pentan-3-one (4). A portion of the 1-hydroxy-4-methyl-1-(*p*-nitrophenyl)-pentan-3-one (**4**) solution in toluene, pyridine, and methyl *tert*-butyl ether was concentrated to a solid. This was recrystallized from toluene and heptane: mp 64−65 °C; ^{1}H NMR (DMSO-d_6) δ 0.93, 0.98 (d,d, 6H), 2.45−2.95 (m, 3H), 5.11 (m, 1H), 5.62 (d, 1H), 7.62 (d, 2H), 8.17 (d, 2H); HPLC 99.2 area %. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.67, H, 6.20; N, 5.76.

1-Acetoxy-4-methyl-1-(*p*-nitrophenyl)pentan-3-one (5). A portion of the 1-acetoxy-4-methyl-1-(*p*-nitrophenyl)pentan-3-one (**5**) solution in toluene and methyl *tert*-butyl ether was concentrated to an oil. On standing, crystals were formed. A portion was recrystallized from toluene and heptane: mp 54−55 °C; ^{1}H NMR ($CDCl_3$) δ 1.04,1.11 (d,d, 6H); 2.07 (s, 3H), 2.57 (h, 1H), 2.86 (*A*BX, 1H), 3.19 (A*B*X, 1H), 6.25 (AB*X*, 1H), 7.54 (d, 2H), 8.21 (d, 2H); HPLC 99.6 area %. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.32, H, 5.95; N, 4.97.

1-(*p*-*N*-Acetylaminophenyl)-4-methylpentan-3-one (7). Crude 1-(*p*-*N*-acetylaminophenyl)-4-methylpentan-3-one **(7)** was recrystallized from ether followed by recrystalliation from ether and heptane: mp 76−77 °C; ^{1}H NMR (DMSO-d_6) δ 0.93 (d, 6H), 1.98 (s, 3H), 2.45−2.8 (m, 5H), 7.07 (d, 2H), 7.42 (d, 2H), 9.80 (s, 1H); HPLC 97.2 area %.

3-Hydroxy-3-isopropyl-5-(*p*-nitrophenyl)-4-pentenoic Acid Benzyl Ester (**10**)**.** A small portion of the crude 3-hydroxy-3-isopropyl-5-(*p*-nitrophenyl)-4-pentenoic acid benzyl ester (**10**) obtained form the above sequence was partitioned between toluene and water. The toluene solution was extracted with water and concentrated to an oil that solidified on standing. The solid was recrystallized from toluene and heptane: mp 57−58 °C; HPLC*:* 99.0 area %; ^{1}H NMR (DMSO-d_6) δ 0.85 (d,d, 6H), 1.85 (h, 1H), 2.68 (AB, 2H), 4.91 (s, 1H), 5.01 (s, 2H), 6.66 (s, 2H), 7.25 (s, 5H), 7.60 (d, 2H), 8.14 (d, 2H). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28, H, 6.28; N, 3.79. Found: C, 68.16, H, 6.15; N, 3.70.

3-Acetoxy-3-[2-(*p*-*N*-acetylaminophenyl)ethyl]-4-methylpentanoic Acid (12). 3-[2-(*p*-Acetylaminophenyl)ethyl]-3-hydroxy-4-methylpentanoic acid **(1a)** (5.87 g) and sodium acetate (0.18 g) were added to THF (35 mL), and the mixture was treated with acetic anhydride (2.25 g) and stirred at rt. After a few minutes the mixture became thick, and more THF (15 mL) was added to facilitate stirring. Stirring was continued overnight to give a solution. Ethyl acetate (25 mL) and water (10 mL) were added and the layers separated. The organic layer was extracted with water (10 mL) and concentrated to about 25 mL, and additional water was

separated. The organic layer was treated with ethyl acetate (50 mL) and toluene (25 mL) and concentrated to about 30 mL. Standing gave crystals which were collected and vacuum-dried to give 4.5 g of 3-acetoxy-3-[2-(*p*-*N*-acetylaminophenyl)ethyl]-4-methylpentanoic acid **(12)**: mp 112−114 °C; ^{1}H NMR (DMSO-d_6) δ 0.90, 0.92 (d,d, 6H), 1.95, 1.99 (s,s, 6H), 2.0−2.6 (m, 7H), 7.06 (d, 2H), 7.43 (d, 2H), 9.83 (s, 1H); MS (DCI, isobutane) 336 (M + 1).

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