Synthetic Applications of Baylis–Hillman Chemistry: An Efficient and Solely Stereoselective Synthesis of (*E*)-α-Methylcinnamic Acids and Potent Hypolipidemic Agent LK-903 from Unmodified Baylis–Hillman Adducts[1)]

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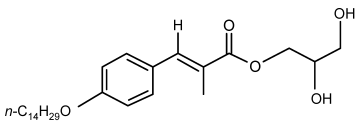
An efficient and solely stereoselective synthesis of (*E*)-α-methylcinnamic acids has been accomplished in single pot by reduction of the unmodified Baylis–Hillman adducts, methyl-3-hydroxy-3-aryl-2-methylenepropanoates with I_2/$NaBH_4$ reagent system at room temperature followed by hydrolysis. The efficacy of this method has been proved in the total synthesis of 1-[*p*-(myristyloxy)-α-methylcinnamoyl]glycerol, LK-903, a highly active hypolipidemic agent.

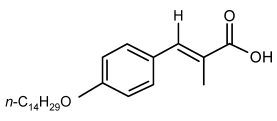
Key words (*E*)-α-methylcinnamic acid; stereoselective synthesis; Baylis–Hillman adduct; hypolipidemic agent; LK-903

α-Methylcinnamic acids and their derivatives possess interesting as well as important biological profiles.[2,3)] Thus, various pharmaceutically potent molecules contain α-methylcinnamic acid moiety as the key structural unit.[2,3)] For example, 1-[*p*-(myristyloxy)-α-methylcinnamoyl]glycerol, **1** (LK-903) is very active hypocholesterolemic agent.[2)] Its corresponding parent acid (*E*)-*p*-myristyloxy-α-methylcinnamic acid (**2**) also shows good hypolipidemic activity.[2)] Biological properties of these compounds mostly depend on the stereochemistry of the double bond of the cinnamic acid moiety.[2,3)] Therefore, development of a simple and efficient method for the stereoselective synthesis of (*E*)-α-methylcinnamic acids and their derivatives is an interesting problem in organic synthesis.[4—7)]

As a part of our continued interest in synthetic applications of the Baylis–Hillman reaction,[8—14)] we envisaged a simple synthesis of (*E*)-α-methylcinnamic acids directly from unmodified Baylis–Hillman adducts.



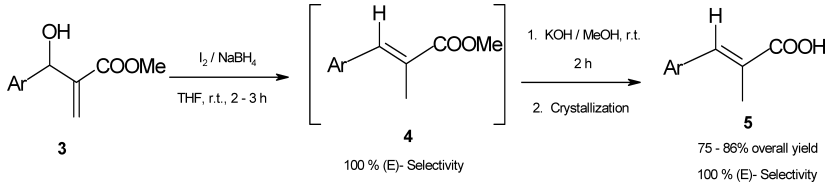
1 LK-903



2

The Baylis–Hillman reaction is a versatile and atom economic carbon–carbon bond forming reaction that provides poly-functional molecules known as Morita–Baylis–Hillman adducts.[15,16)] These adducts have been employed for the stereoselective synthesis of various naturally occurring bioactive compounds[16—19)] including several alkaloids,[20)] terpenoids,[21,22)] macrolides[23)] and pheromones.[24,25)] All of these molecules contain a stereodefined α,β-unsaturated carbonyl moiety as the central structural unit which have been well documented in the literature.[16)] We herein, wish to report an efficient one-pot and solely stereoselective synthesis of (*E*)-α-methylcinnamic acids directly from unmodified Baylis–Hillman adducts. We observed that the treatment of Baylis–Hillman adduct, methyl-3-hydroxy-3-aryl-2-methylenepropanoates **3** with $NaBH_4$ in combination with molecular I_2 in tetrahydrofuran (THF) at room temperature, followed by hydrolysis with KOH/MeOH and crystallization afforded the corresponding (*E*)-α-methylcinnamic acids **5** in high yields *via* the formation of the intermediates **4** (Chart 1).

Previously, α-methylcinnamic acids were not obtained directly from the unmodified Baylis–Hillman adducts.[26)] One modified version (acetyl derivative) of the Baylis–Hillman adduct was used in that case[26)] which required three steps to get the desired product starting from the adduct itself. Being intrigued with this fact, and after systematic literature survey,[16)] it became clear that, synthesis of the desired trisubstituted olefin moiety directly from the unmodified Baylis–Hillman adducts is significantly challenging task compared to that from an activated version (acetyl or allyl bromide derivatives) of the adducts.[27)] The present method is more advantageous and easily accessible to α-methylcinnamic acids as they have been accomplished directly from unmodified Baylis–Hillman adducts with sole (*E*)-stereoselectivity (Chart 1). Here, initially we treated **3b** (Ar=2-Cl–C_6H_4) with $NaBH_4$ in presence of I_2 in THF at room temperature. The mode of addition of reagents was found to be important for achieving optimum yields. The addition of $NaBH_4$ (2 eq) into the homogeneous mixture of adduct (1 eq) and iodine (2 eq) in THF was preferred in terms of yields of



3 **4** 100 % (E)- Selectivity **5** 75 - 86% overall yield 100 % (E)- Selectivity

Chart 1

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the product as the addition of adduct to the I_2/$NaBH_4$ reagent or its reverse addition resulted in the lowering of the yield. The reaction was completed within 2 h to afford **4b** with sole (*E*)-selectivity as indicated by its ^{1}H-NMR spectrum which showed the presence of the deshielded olefinic proton at δ 7.72 (1H, s).[28,29] Compound **4b** was then treated with KOH/MeOH for 2 h at room temperature in the same reaction vessel and the product was crystallized from hexane–EtOAc (1 : 1) to afford pure **5b** (overall yield: 82%). Subsequently a series of (*E*)-α-methylcinnamic acids **5a**—**h**, **2** (Table 1) were prepared in single-pot directly from various adducts **3a**—**i** without isolating the intermediates **4**. The yields of the products were high (75—86%) with respect to the adducts **3** and they were formed with solely (*E*)-stereoselectivity. The reducing system I_2/$NaBH_4$ is known to generate diborane *in situ* which is possibly working here as a source of hydride nucleophile.[30]

The structures and stereochemistry of the products were settled from their spectral (^{1}H- and ^{13}C-NMR, MS) and analytical data. The stereochemistry of the product can be explained by considering the transition state models **A** and **B** (Fig. 1). The transition state **A** is more favored than **B** and (*E*)-products are thus formed exclusively.

Table 1. Synthesis of (*E*)-α-Methylcinnamic Acids (**5**) Using I_2/$NaBH_4$[a,b]

Entry	Ar	(*E*)-α-Methyl cinnamic acids (**5**)	Isolated yield (%)[c]
3a	C_6H_5	**5a**	86
3b	2-Cl–C_6H_4	**5b**	82
3c	4-Me–C_6H_4	**5c**	81
3d	4-MeO–C_6H_4	**5d**	78
3e	4-Cl–C_6H_4	**5e**	77
3f	2,4-Cl_2–C_6H_3	**5f**	80
3g	3-Cl–C_6H_4	**5g**	76
3h	3,4-O–CH_2–O–C_6H_3	**5h**	73
3i	4-(*n*-$C_{14}H_{29}$)–O–C_6H_4	**2**	75

a) The structures of the compounds (**5**) were determined from their spectral (^{1}H-, ^{13}C-NMR and MS) and analytical data; (*E*)-stereochemistry was assigned on the basis of the chemical shift value of the vinylic proton in ^{1}H-NMR spectra. *b*) Hydrolysis of intermediate ester (**4**) was carried out with 60% KOH in MeOH for 2 h at r.t. *c*) Isolated yield was calculated with respect to the corresponding adducts (**3**).

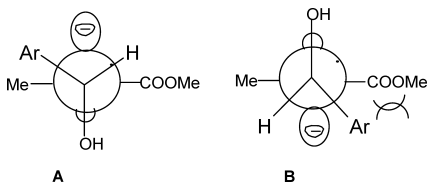
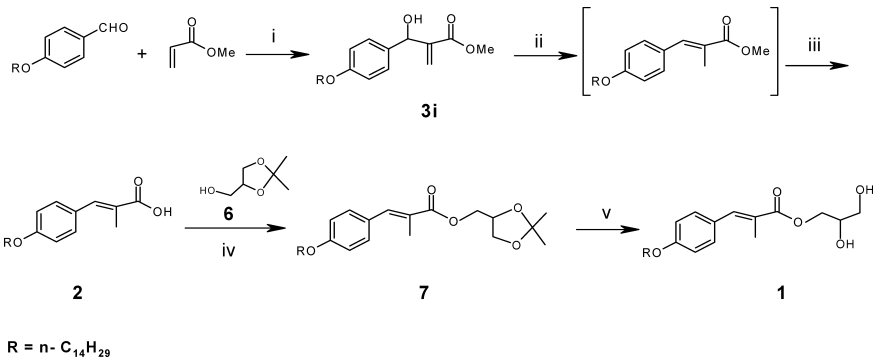


Fig. 1

Previously, esterification of the acid (**2**) with 2,3-acetonide protected glycerol **6** (Chart 2) was carried out classically by converting the acid into corresponding acid chloride.[2] Under this classical condition, the yield of the ester **7** was only 70%. During the portion-wise addition of acetonide protected glycerol (**6**) to the acid chloride, the byproduct was HCl acid which might be causing the deprotection of the acid sensitive acetonide group lowering the yield of the ester.[2] To avoid this problem, we undertook a straightforward strategy involving the direct coupling of acid **2** and alcohol **6** for esterification applying a recently reported protocol using BOC_2O and DMAP[31] as coupling reagents. Purification of the ester **7** is easier by this method since the byproducts, *t*-BuOH and CO_2 are volatile which is a great advantage over the classical method.[31] Subsequent deprotection of the acetonide group of the prepared ester **7** with Amberlyst-15 (solid acid catalyst) yielded the target molecule LK-903 (**1**) in 94% yield and 100% (*E*)-selectivity (Chart 2). Previously this final deprotection step was done under homogeneous acid (H_3BO_3) catalyzed condition and yield was only 72%.[2]

In conclusion, we have described a novel and efficient one-pot method for the stereoselective synthesis of (*E*)-α-methylcinnamic acids directly from unmodified Baylis–Hillman adducts. The method is associated with several advantages including mild reaction conditions, application of inexpensive and easily available reagents, operational simplicity, high yields and excellent stereoselectivity. Moreover, the present method is more atom economic and useful application of Baylis–Hillman chemistry regarding the synthesis of (*E*)-α-methylcinnamic acids compared to the previous reports. The method has successfully been applied in the total synthesis of LK-903, a highly potent hypolipidemic agent which has not been synthesized with sole (*E*)-stereoselectiv-



Reagents and conditions: i) DABCO, dioxane/water (1 : 1), r.t., 7 d, 73%; ii) I_2 (2 eq)/$NaBH_4$ (2 eq), THF, r.t., 3 h; iii) 60% KOH in MeOH, 2 h, r.t., dilute. HCl; crystallization (hexane–EtOAc, 1 : 1) 75% (from **3i**); iv) BOC_2O, DMAP, THF, r.t., 16 h, 92%; v) Amberlyst-15, MeOH, r.t., 2 h, 94%.

Chart 2

ity previously.[2] Thus, unlike the classical approach, we have given a modern approach in every step of its synthesis to enhance the overall yield and stereoselectivity of the target molecule.

Experimental

Synthesis of Baylis–Hillman Adduct 3i A solution of 4-(myristyloxy) benzaldehyde (6.36 g, 20 mmol) and methyl acrylate (5.36 ml, 60 mmol) in 50 ml of 1 : 1 dioxane–water (v/v) was stirred at room temperature in the presence of 100 mol% DABCO (2.24 g, 20 mmol). The reaction progress was monitored by thin layer chromatography. Upon completion (7 d) the reaction mixture was partitioned with *tert*-butylmethyl ether (500 ml) and water (150 ml). The organic phase was washed with brine (2×80 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (12% EtOAc in hexane) to give the adduct **3i**. Colorless powder, yield 5.9 g (73%).

General Procedure for the One-Pot Synthesis of (*E*)-α-Methylcinnamic Acids To a solution of Baylis–Hillman adduct **3** (5 mmol, 1 eq) in anhydrous THF (10 ml) molecular I_2 (10 mmol, 2 eq) was added and the mixture was stirred for 5 min at room temperature under nitrogen atmosphere. $NaBH_4$ (10 mmol, 2 eq) was then added portion-wise to this mixture and stirring was continued. Slow gas evaluation occurred with a little increase in temperature and the brown solution was slowly turned colorless. The reaction was monitored by TLC. After completion, THF was evaporated and 60% KOH (3 g) in MeOH (5 ml) was added. The mixture was again stirred for 2 h at room temperature. MeOH was removed under reduced pressure. The residue was diluted with water (10 ml), acidified with dilute HCl (1 N) and extracted with ether (3×20 ml). The extract was dried over Na_2SO_4 and concentrated. The crude product was crystallized from hexane–EtOAc (1 : 1) to afford pure (*E*)-α-methylcinnamic acid. The spectroscopic (^{1}H-, ^{13}C-NMR and MS) and analytical data of some representative compounds are given below.

5b: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ: 7.92 (1H, s), 7.50—7.21 (4H, m), 2.02 (3H, s); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ: 174.1, 138.4, 134.2, 131.3, 130.5, 130.0, 128.2, 126.8, 126.4, 13.8; EI-MS: *m*/*z* 198, 196 ($M^{+\cdot}$), 161, 115; *Anal.* Calcd for $C_{10}H_9ClO_2$: C, 61.22; H, 4.59%. Found: C, 61.16; H, 4.62%.

5d: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ: 7.78 (1H, s), 7.44 (2H, d, J=8.0 Hz), 6.90 (2H, d, J=8.0 Hz), 3.82 (3H, s) 2.10 (3H, s); EI-MS: *m*/*z* 192 ($M^{+\cdot}$), 146, 121; *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25%. Found: C, 68.82; H, 6.21%.

2: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ: 7.69 (1H, s), 7.33 (2H, d, J=8.0 Hz), 6.81 (2H, d, J=8.0 Hz), 3.90 (2H, t, J=7.0 Hz), 2.10 (3H, s), 1.75—1.66 (2H, m), 1.48—1.32 (2H, m), 1.31—1.14 (20H, m), 0.82 (3H, t, J=7.0 Hz); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ: 174.5, 159.6, 141.0, 131.8, 126.2, 125.2, 114.6, 68.3, 32.0, 29.8, 29.5, 29.3, 26.1, 22.8, 14.2, 13.8; FAB-MS: *m*/*z* 375 ($M^{+\cdot}$+1); *Anal.* Calcd for $C_{24}H_{38}O_3$: C, 77.00; H, 10.16%. Found: C, 77.24; H, 10.22%.

Esterification of 2 with Acetonide Protected Glycerol 6 A dried flask was charged with **2** (748 mg, 2 mmol), acetonide protected glycerol **6**[31] (343 mg, 2.6 mmol), DMAP (12 mg, 0.1 mmol) and BOC_2O (585 mg, 2.6 mmol). Dry THF (5 ml) was added by syringe and the mixture was stirred at 50 °C. After completion of the reaction (monitored by TLC) EtOAc (10 ml) was added and the organic layer was washed consecutively with HCl (2 N), $NaHCO_3$ solution, water and brine and subsequently dried. The volatiles were removed *in vacuo* and the residue was subjected to column chromatography over silica gel using 18% EtOAc in hexane as eluent to obtain pure **7** (898 mg, 92%); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ: 7.63 (1H, s), 7.32 (2H, d, J=8.0 Hz), 6.84 (2H, d, J=8.0 Hz), 4.33 (1H, m), 4.21 (2H, d, J=5.5 Hz), 4.09 (1H, dd, J=12.0, 2.0 Hz), 3.95 (2H, t, J=7.0 Hz), 3.78 (1H, dd, J=12.0, 2.0 Hz), 2.12 (3H, s), 1.82—1.72 (2H, m), 1.41 (3H, s), 1.31 (3H, s), 1.30—1.18 (22H, m), 0.86 (3H, t, J=7.0 Hz); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ: 168.9, 159.5, 139.6, 132.0, 129.8, 128.2, 114.6, 109.7, 68.1, 67.2, 67.1, 64.9, 32.1, 29.8, 29.4, 27.5, 26.8, 25.2, 22.8, 14.0; EI-MS: *m*/*z* 488 ($M^{+\cdot}$), 433, 357, 250, 119; *Anal.* Calcd for $C_{30}H_{48}O_5$: C, 73.77; H, 9.84%. Found: C, 73.64; H, 9.92%.

Acetonide Deprotection of 7 To a solution of **7** (488 mg, 1 mmol) in MeOH (5 ml) Amberlyst-15 (100 mg) was added. The mixture was stirred at room temperature for 2 h. Amberlyst-15 was removed by filtration and the filtrate was concentrated. The residue was subjected to column chromatography over silica gel using 40% EtOAc in hexane to afford pure **1** (421 mg, 94%); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ: 7.68 (1H, s), 7.49 (2H, d, J=8.0 Hz), 6.90 (2H, d, J=8.0 Hz), 4.35 (1H, m), 4.06—3.92 (3H, m), 3.80—3.58 (3H, m), 2.19 (3H, s), 1.90—1.76 (2H, m), 1.49—1.20 (22H, m), 0.92 (3H, t, J=7.0 Hz); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ: 169.6, 159.8, 139.9, 131.9, 130.0, 128.1, 114.6, 70.7, 68.2, 65.7, 63.4, 32.0, 29.8, 29.6, 29.2, 27.3, 22.6, 14.1; EI-MS: *m*/*z* 448 ($M^{+\cdot}$), 357, 279, 159; *Anal.* Calcd for $C_{27}H_{44}O_5$: C, 72.32; H, 9.82%. Found: C, 72.44; H, 9.76%.

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References and Notes

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