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# A facile one-pot stereoselective synthesis of trisubstituted (*E*)-2-methylalk-2-enoic acids from unactivated Baylis–Hillman adducts and a simple access to some important insect pheromones☆

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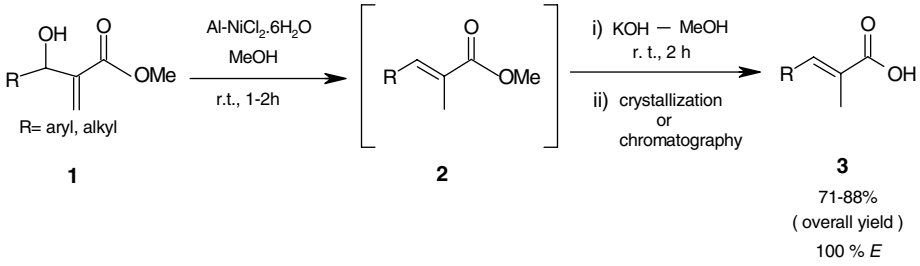
**Abstract**—An efficient one-pot stereoselective synthesis of trisubstituted (*E*)-2-methylalk-2-enoic acids has been accomplished by treatment of unactivated Baylis–Hillman adducts, 3-hydroxy-2-methylenealkanoates, with Al–$NiCl_2{\cdot}6H_2O$ in methanol at room temperature followed by hydrolysis. The method has been applied to the synthesis of three important insect pheromones, (4*S*,2*E*)-2,4-dimethyl-2-hexenoic acid, (+)-(*S*)-manicone and (+)-(*S*)-normanicone.


The Baylis–Hillman reaction is a versatile carbon–carbon bond forming reaction, which provides functionalized adducts.[1] These adducts have been utilized in various synthetic transformations and also in stereoselective syntheses of several naturally occurring bioactive compounds.[1b,2] In continuation of our work[2c,3] on Baylis–Hillmann chemistry, we have recently observed that treatment of unactivated Baylis–Hillman adducts, that is, 3-hydroxy-2-methylenealkanoates **1** with Al–$NiCl_2{\cdot}6H_2O$ in methanol at room temperature followed by hydrolysis with KOH/MeOH produced the corresponding trisubstituted (*E*)-2-methylalk-2-enoic acids **3** via formation of the intermediate esters **2** (Scheme 1). The core structure of the acids **3** is present in various bioactive α-methylcinnamic acids[4] (for example, in LK 903, a hypolipidemic agent) and in several insect pheromones[5,6] (such as (4*S*,2*E*)-2,4-dimethyl-2-hexenoic acid) (Fig. 1). The present method is a simple access to these important compounds.

Initially we treated **1a** (R = $C_6H_5$) with various reducing systems in different solvents under different reaction conditions (Table 1). Al–$NiCl_2{\cdot}6H_2O$ proved to be best reducing system at room temperature in methanol




**Scheme 1.**

*Keywords*: Baylis–Hillman adduct; Al–$NiCl_2{\cdot}6H_2O$; (*E*)-2-Methylalk-2-enoic acid; Stereoselectivity; Pheromone.
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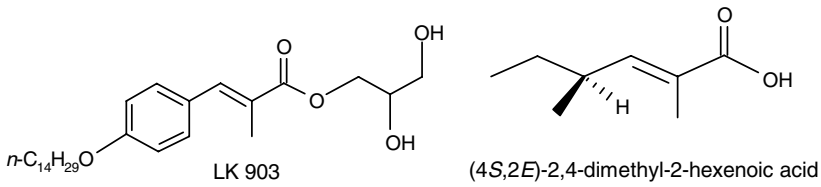



**Figure 1.**

**Table 1.** Reaction of **1a** ($R = C_6H_5$) with different reducing systems

| Entry | Reagent | Solvent | Time (h) | Isolated Yield(%) |
|---|---|---|---|---|
| a | Zn–$NH_4Cl$ | $H_2O$ | 18 | 58[a,b] |
| b | Zn–AcOH | $CH_2Cl_2$ | 5 | 41[c] |
| c | In–$NH_4Cl$ | EtOH–$H_2O$ (1:1) | 9 | 19[a] |
| d | Mg | MeOH | 3 | 17 |
| e | Zn–Cu | MeOH–$H_2O$ (3:1) | 4 | 38[a,d] |
| f | Al–$NiCl_2{\cdot}6H_2O$ | MeOH | 1 | 99[e] |
| g | Al–$NiCl_2{\cdot}6H_2O$ | THF | 1 | 98[e] |
| h | Al–$NiCl_2$ | MeOH | 1 | 0 |

[a] Reaction mixture was refluxed.
[b] An unidentified side product was obtained.
[c,d,e] *E*/*Z* ratio was 58:42, 60:40, and 100:0, respectively (determined from $^1H$ NMR spectra of the crude products).

affording **2a** in 1 h in a very high yield (99%) and with complete *E*-selectivity. THF was also found to be a suitable solvent for the reaction. However, as we intended to hydrolyze the intermediate ester **2a** without isolation, the reaction was carried out in MeOH.

A series of (*E*)-2-methylalk-2-enoic acids were subsequently prepared in one-pot from Baylis–Hillman adducts, **1** (derived from both aromatic and aliphatic aldehydes) by treatment with Al–$NiCl_2{\cdot}6H_2O$ in methanol at room temperature and hydrolyzing the intermediate esters with KOH–MeOH (Table 2).[7] The final products were purified by crystallization or column chromatography. The yields of the products were high (71–88% with respect to the adducts **1**) and were formed solely with (*E*)-stereoselectivity. The structures and stereochemistries of the products were confirmed from their spectral (IR, $^1H$, and $^{13}C$ NMR and MS) and microanalytical data.[7] In the $^1H$ NMR spectrum of a trisubstituted alkene, the β-vinylic protons, cis and trans to the ester group are known to resonate at $\delta$ 7.5 and 6.5, respectively, when R is an aryl group.[8] The same proton cis and trans to an ester group appears at $\delta$ 6.8 and 5.7, respectively, when R is alkyl.[8] These values were useful in determining the stereochemistry of the products.

Al–$NiCl_2{\cdot}6H_2O$ was initially used for the reduction of α,β-unsaturated carbonyl compounds to produce the corresponding saturated carbonyl compounds.[9] The proposed mechanism involves the interaction of Al with $NiCl_2$ to form Ni(0), which then loses electrons. However, in the present case, isomerization of the exocyclic double bond with concomitant loss of C-3–OH took place. The stereochemistry of the reaction can possibly be explained[2b,d,3a,b] by considering the transition state models **A** and **B** (Fig. 2). Transition state **A** is more favored than **B**- and (*E*)-products are thus formed solely.

**Table 2.** Synthesis of trisubstituted (*E*)-2-methylalk-2-enoic acids **3** using Al–$NiCl_2{\cdot}6H_2O$

| Entry | R | Time (h)[a] | Isolated yield[b,c,d] (%) |
|---|---|---|---|
| a | $C_6H_5$ | 1 | 88 |
| b | 4-$MeC_6H_4$ | 1 | 84 |
| c | 4-$EtC_6H_4$ | 1.5 | 83 |
| d | 4-$ClC_6H_4$ | 1 | 81 |
| e | 2,4-$Cl_2C_6H_3$ | 1 | 86 |
| f | 3,4,5-$(MeO)_3C_6H_2$ | 2 | 71 |
| g | 4-$C_{14}H_{29}OC_6H_4$ | 2 | 78 |
| h | $C_2H_5$ | 2 | 77 |
| i | *i*-Pr | 2 | 75 |
| j | *n*-$C_5H_{11}$ | 2 | 74 |
| k | *n*-$C_7H_{15}$ | 2 | 72 |

[a] Time required for reduction of the adduct. The time required for hydrolysis is 2 h in each case and is not included here.
[b] The acids were purified by column chromatography using hexane–EtOAc (4:1) when R = alkyl or by crystallization from hexane–EtOAc (1:1) when R = aryl.
[c] All products were characterized by $^1H$ and $^{13}C$ NMR, MS, and IR data.
[d] *E*/*Z* ratio was 100:0.

The present method is useful for the synthesis of (*E*)-α-methylcinnamic acids (R = aryl in **3**) and insect pheromones (R = alkyl in **3**). Unmodified adducts can directly be used for the preparation of these compounds. The present methodology was also successfully employed for the synthesis of (4*S*,2*E*)-2,4-dimethyl-2-hexenoic acid **4** (a caste-specific compound of the mandibular glands of male carpenter ants of the genus *Camponotus*)[5] from the adduct[10] **5** derived from (*S*)-2-methylbutyraldehyde[11] (Scheme 2). Adduct **5** was formed as an inseparable mixture of *syn*- and *anti*-isomers in a 70:30 ratio.[10] Reduction of **5** with migration of the double bond and subsequent elimination of the hydroxyl group

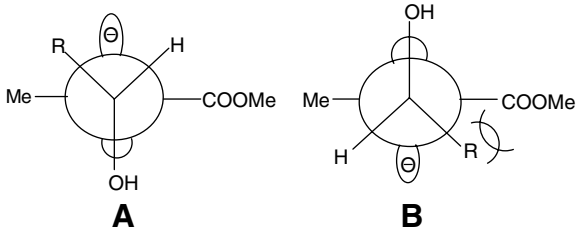
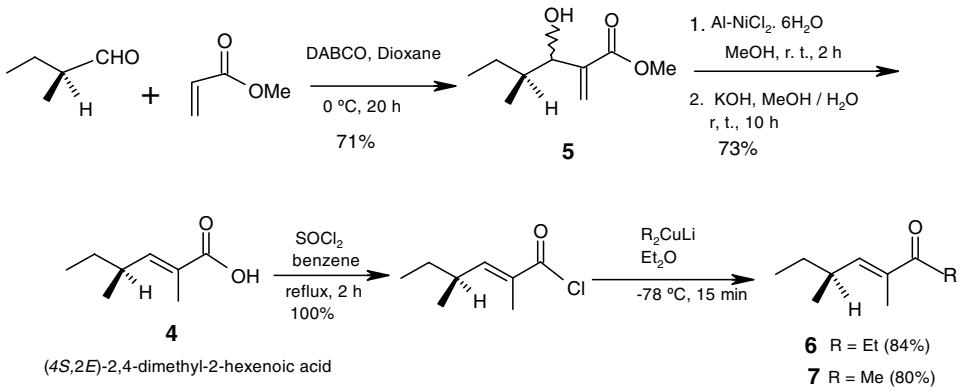



**Figure 2.**




**Scheme 2.**

would lead to loss of the stereogenic centre at C-3. Hence, no attempt was made to separate the diastereomers of **5**. Acid **4** was subsequently converted into (+)–(*S*)-manicone **6** and (+)-(*S*)-normanicone **7** (the mandibular gland alarm pheromone substances of the ants of the genus *Manica*)[6] by treating the corresponding acid chlorides with $Et_2CuLi$ and $Me_2CuLi$ separately in ether solution at −78 °C.[11] The optical and spectral properties ($^1H$ and $^{13}C$ NMR and MS) of **4**, **6**, and **7** were in good agreement with those reported earlier.[11,12]

Alternative methods for the synthesis of 2-methylalk-2-enoic acids are the Wittig reaction and the Horner–Wadsworth–Emmons reaction. The latter method is an improved protocol of the former and more advantageous as the phosphate by-product can be extracted into water.[13] 2-Methylalk-2-enoic acids and related compounds including manicone (**6**) were prepared earlier employing the Horner–Wadsworth–Emmons method.[14a] However, the required α-branched diethylcarboxylic methane phosphonates are not commercially available and the preparation of these compounds involved complex experimental steps.[14b] The reactions between phosphonates and aldehydes required a low temperature (−60 °C). In the present method for the preparation of 2-methylalk-2-enoic acids, all the reagents were directly available and the reactions were conducted at room temperature. Using the Horner–Wadsworth–Emmons method, the 2-methylalk-2-enoic acids derived from aliphatic aldehydes were mixtures of (*E*)- and (*Z*)-isomers. Manicone, prepared by this method, was also obtained as a mixture of (*E*)- and (*Z*)-isomers. In the present method the products were formed solely as the (*E*)-isomers. Thus, the present method is superior to classical alternatives.

In conclusion, we have developed a simple and efficient method for the synthesis of trisubstituted (*E*)-2-methylalk-2-enoic acids from unmodified Baylis–Hillman adducts by treatment with Al–$NiCl_2{\cdot}6H_2O$ at room temperature followed by hydrolysis with KOH–MeOH. The high yields and excellent stereoselectivity are advantages of this method. The method has successfully been applied to the synthesis of some important insect pheromones.

## Acknowledgement

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## References and notes

1. (a) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q; (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891, and references cited therein.
2. (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94–110; (b) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213–1220; (c) Das, B.; Banerjee, J.; Mahender, G.; Majhi, A. *Org. Lett.* **2004**, *6*, 3349–3352; (d) Chandrasekhar, S.; Chandrasekhar, G.; Vijeender, K.; Reddy, M. S. *Tetrahedron Lett.* **2006**, *47*, 3475–3478.
3. (a) Das, B.; Banerjee, J.; Ravindranath, N. *Tetrahedron* **2004**, *60*, 8357–8361; (b) Das, B.; Banerjee, J.; Majhi, A.; Mahender, G. *Tetrahedron Lett.* **2004**, *45*, 9225–9227; (c) Das, B.; Majhi, A.; Banerjee, J.; Chowdhury, N.; Venkateswarlu, K. *Tetrahedron Lett.* **2005**, *46*, 7913–7915; (d) Das, B.; Holla, H.; Majhi, A.; Venkateswarlu, K. *Tetrahedron Lett.* **2005**, *46*, 8895–8897.
4. Basavaiah, D.; Krishnamacharyulu, M.; Hyma, R. S.; Sarma, P. K. S.; Kumaragurabaran, N. *J. Org. Chem.* **1999**, *64*, 1197–1200.
5. Brand, J. M.; Duffield, R. M.; MacConnell, J. G.; Blum, M. S.; Fales, H. M. *Science* **1973**, *179*, 388–389.
6. (a) Fales, H. M.; Blum, M. S.; Crewe, R. M.; Brand, J. M. *J. Stored. Prod. Res.* **1972**, *18*, 1077; (b) Bestmann, H. J.; Attygalle, A. B.; Glasbrenner, J.; Reimer, R.; Vostrowsky, O. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 784.
7. General experimental procedure: To a mixture of fresh Al powder (20 mmol) and $NiCl_2{\cdot}6H_2O$ (20 mmol) was added the Baylis–Hilmann adduct **1** (2 mmol) dissolved in freshly distilled MeOH (10 mL). A vigorous reaction took place within a few seconds, which subsided after 20 min. The reaction was monitored by TLC. After completion, 60% KOH (3 g) in MeOH (5 mL) was added and the reaction stirred for 2 h at room temperature. MeOH was removed under reduced pressure and the reaction mixture was diluted with water (100 mL) and filtered. The filtrate was acidified with dilute HCl (1 N) and extracted with ether (2 × 50 mL). The ether extract was dried over $Na_2SO_4$ and

concentrated. The crude product was purified by crystallization from hexane–EtOAc (1:1) (when **1** was derived from an aromatic aldehyde) or by column chromatography over silica gel using 10% EtOAc in hexane as eluent (when **1** was derived from an aliphatic aldehyde).

The spectral (IR, $^1$H and $^{13}$C NMR and MS) and analytical data of the novel (*E*)-2-methylalk-2-enoic acids are given below.

*Product* **3c**: IR (KBr): $\nu_{max}$ 3417, 1682, 1617 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.81 (1H, s), 7.37 (2H, d, $J = 8.0$ Hz), 7.21 (2H, d, $J = 8.0$ Hz), 2.69 (2H, q, $J = 7.0$ Hz), 2.15 (3H, s), 1.28 (3H, t, $J = 7.0$ Hz); $^{13}$C NMR (50 MHz, $CDCl_3$): 174.8, 142.2, 141.5, 133.1, 130.2, 128.3, 126.9, 28.3, 15.4, 14.2; FABMS: *m*/*z* 191 $[M+H]^{+\cdot}$. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.79; H, 7.37. Found: C, 75.86; H, 7.31.

*Product* **3f**: IR (KBr): $\nu_{max}$ 2962, 1688, 1612 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.73 (1H, s), 6.62 (2H, s), 3.88 (9H, s), 2.16 (3H, s); $^{13}$C NMR (50 MHz, $CDCl_3$): 174.3, 153.6, 136.8, 132.3, 107.7, 55.8, 14.6; FABMS: *m*/*z* 253 $[M+H]^{+\cdot}$, Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.91, 6.35. Found: C, 61.82, 6.41.

*Product* **3j**: IR (KBr): $\nu_{max}$ 3412, 1688, 1612 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 11.92 (1H, br s), 6.88 (1H, t, $J = 7.0$ Hz), 2.21 (2H, q, $J = 7.0$ Hz), 1.89 (3H, s), 1.52–1.40 (2H, m), 1.39–1.26 (4H, m), 0.87 (3H, t, $J = 7.0$ Hz); FABMS: *m*/*z* 157 $[M+H]^{+\cdot}$. Anal. Calcd for $C_9H_{16}O_2$: C, 69.23; H, 10.26. Found: C, 69.31; H, 10.22.

*Product* **3k**: IR (KBr): $\nu_{max}$ 3418, 1689, 1642 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): 6.89 (1H, t, $J = 7.0$ Hz), 2.20 (2H, q, $J = 7.0$ Hz), 1.81 (3H, s), 1.50–1.42 (2H, m), 1.39–1.22 (8H, m), 0.88 (3H, t, $J = 7.0$ Hz); FABMS: *m*/*z* 185 $[M+H]^{+\cdot}$. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.74; H, 10.87. Found: C, 71.68; H, 10.92.


8. (a) Larson, G. L.; de Kaifer, C. F.; Seda, R.; Torres, L. E.; Ramirez, J. R. *J. Org. Chem.* **1984**, *49*, 3385–3388; (b) Basavaiah, D.; Sarma, P. K. S.; Bhavani, A. K. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1091–1092; (c) Baraldi, P. G.; Guarneri, M.; Pollini, G. P.; Simoni, D.; Barco, A.; Benetti, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2501–2505; (d) Tanaka, K.; Yamagishi, N.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3619–3625.
9. (a) Hazarika, M. J.; Barua, N. C. *Tetrahedron Lett.* **1989**, *30*, 6567–6570; (b) Sarmah, B. K.; Barua, N. C. *Tetrahedron* **1991**, *47*, 8587–8600.
10. Preparation of Baylis–Hillman adduct **5** (methyl-3-hydroxy-4-methyl-2-methylene-2-hexenoate): A solution of (*S*)-2-methylbutyraldehyde (1.08 mL, 10 mmol) and methyl acrylate (2.68 mL, 30 mmol) in dioxane (10 mL) was cooled to 0 °C and DABCO (50 mol %, 0.56 g, 10 mmol) was added. After completion (20 h), the reaction was partitioned with *tert*-butylmethyl ether (75 mL) and 5% aqueous HCl solution (25 mL). The organic extracts were collected, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography (5% EtOAc in hexane) to give adduct **5** (1.22 g, colorless oil) as an inseparable mixture of *syn*/*anti* isomers (70:30, 71% combined yield). The ratio was assigned from the $^1$H NMR chemical shifts and coupling constant values of the C3-H and C4-H. See: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, 1984; Vol. 3, pp 111–118. IR (KBr): $\nu_{max}$ 3485, 2965, 2932, 2880, 1726, 1631 cm$^{-1}$; $^1$H NMR: $\delta$ 0.80–0.96 (6H, m), 1.15 (1.4H, m, *syn*), 1.43 (0.6H, m, *anti*), 1.68 (1H, m), 2.60 (0.7H, d, $J = 6.5$ Hz, *syn*), 2.83 (0.3H, d, $J = 8.0$ Hz, *anti*), 3.76 (3H, s), 4.08 (0.3H, t, $J = 8.0$ Hz, *anti*), 4.30 (0.7H, t, $J = 6.5$ Hz, *syn*), 5.74 (0.3H, s, *anti*), 5.79 (0.7H, s, *syn*), 6.24 (0.3H, s, *anti*), 6.27 (0.7H, s, *syn*); $^{13}$C NMR: *syn* $\delta$ 11.9, 13.4, 26.8, 39.0, 52.0, 74.7, 125.6, 142.3, 167.3; *anti* $\delta$ 11.5, 16.0, 24.5, 39.5, 52.0, 76.8, 126.3, 141.9, 167.5; *m*/*z* 173 ($M^{+\cdot}$+1). Anal. Calcd for $C_9H_{16}O_3$: C, 62.79; H, 9.30. Found: C, 62.70; H, 9.34.
11. Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron* **1992**, *48*, 8801–8824.
12. Martischonok, V.; Melikyan, G. G.; Mineif, A.; Vostrowsky, O.; Bestmann, H. J. *Synthesis* **1991**, 560–564.
13. Li, J. J. *Name Reactions*, 2nd ed.; Springer: New Delhi, 2003; pp 198–199.
14. (a) Coutrot, P.; Ghribi, A. *Synthesis* **1986**, 790–792; (b) Coutrot, P.; Ghribi, A. *Synthesis* **1986**, 661.