Synthetic Applications of the *Baylis–Hillman* Reaction: Simple and Convenient Synthesis of Five Important Insect Pheromones[1])

by **Biswanath Das***, **Joydeep Banerjee**, **Nikhil Chowdhury**, **Anjoy Majhi**, and **Gurram Mahender**

Organic Chemistry Division – I, Indian Institute of Chemical Technology, Hyderabad – 500 007, India. (fax : (+91)-40-7160512; e-mail: biswanathdas@yahoo.com)

A simple and convenient synthesis of five important insect pheromones by means of *Baylis–Hillman* adducts is described, *i.e.*, of (2*E*,4*S*)-2,4-dimethylhex-2-enoic acid (**1**), a mandibular-gland secretion of the male carpenter ant in the genus *Camponotus*, of (+)-(*S*)-manicone (**2**) and (+)-(*S*)-normanicone (**3**), two mandibular-gland constituents of *Manica* ants, and of (+)-dominicalure-I (**6**) and (+)-dominicalure-II (**7**), two aggregation pheromones of the lesser grain borer *Rhyzopertha dominica* (F). For the first time, the potential of the *Baylis–Hillman* chemistry for the stereoselective synthesis of trisubstituted olefins was successfully applied to the synthesis of these pheromone compounds.

Introduction. – Trisubstituted alkene moieties have been widely observed in several natural bioactive compounds including different pheromones and antibiotics [1]. The biological properties of these alkenes are remarkably dependent on the configuration of the C=C bond [2]. A number of methods have been developed for the stereoselective synthesis of trisubstituted alkenes [2–6]. As a part of our research program on the synthetic application of the *Baylis–Hillman* reactions [7–9], we herein report the simple and convenient synthesis of five important insect pheromones, *i.e.*, of (2*E*,4*S*)-2,4-dimethylhex-2-enoic acid (**1**), a caste-specific substance present in the mandibular glands of the male carpenter ants in the genus *Camponotus* [10], of (+)-(*S*)-manicone (**2**) and (+)-(*S*)-normanicone (**3**), the mandibular-gland alarm pheromone components of the ants in the genus *Manica* [11][12], and of (+)-(1*S*)-1-methylbutyl (2*E*)-2-methylpent-2-enoate (=dominicalure-I; **6**) and (+)-(1*S*)-1-methylbutyl (2*E*)-2,4-dimethylpent-2-enoate (=dominicalure-II; **7**), the aggregation pheromones of the lesser grain borer *Rhyzopertha dominica* (F) [13].

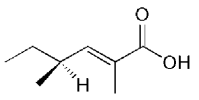
The *Baylis-Hillman* reaction is a versatile C–C bond forming reaction providing synthetically useful multifunctional adducts [14]. These adducts have been successfully utilized for the stereoselective synthesis of various naturally occurring bioactive molecules [14b][15–18]. Most of these molecules contain a configurationally defined trisubstituted C=C bond as the key structural unit which has been well documented in the literature [14b].

Despite these substantial advances in synthetic applications of the *Baylis–Hillman* chemistry, to the best of our knowledge, this is the first report[2]) on the syntheses of the

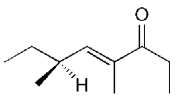
[1]) Part 25 in the series, 'Synthetic studies on natural products'.

[2]) Only the synthesis of racemic compound (±)-**1** from a *Baylis–Hillman* adduct has been reported earlier [6d].

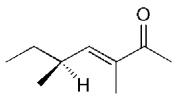
© 2006 Verlag Helvetica Chimica Acta AG, Zürich



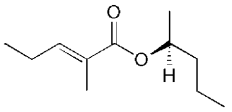
1 (2*E*,4*S*)-2,4-dimethylhex-2-enoic acid



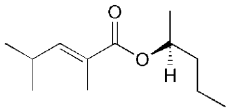
2 (+)-(*S*)-manicone



3 (+)-(*S*)-normanicone



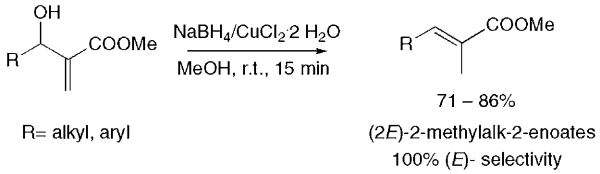
6 (+)-(*S*)-dominicalure-I



7 (+)-(*S*)-dominicalure-II

chiral pheromones **1**–**3**, **6**, and **7** exploring the immense potential of *Baylis–Hillman* adducts for the stereoselective generation of trisubstituted alkene moieties. These chiral pheromones were mainly selected as synthetic targets because of the presence of an (*E*)-configurated C=C bond in their structures which can easily be accessed *via Baylis–Hillman* adducts and which ultimately is responsible for the observed biochemical signalling [4a,b][5b,c][10–13]. Very recently we have developed an efficient and facile stereoselective synthesis [9] of (2*E*)-2-methylalk-2-enoates directly from unmodified *Baylis–Hillman* adducts using inexpensive $NaBH_4$ as hydride donor in the presence of $CuCl_2 \cdot 2H_2O$ in MeOH at room temperature (*Scheme 1*).

Scheme 1. *Stereoselective Synthesis of (2*E*)-2-Methylalk-2-enoates*



While we completed the above work [9], *Fernandes et al.* [6d] reported a synthesis of (±)-**1** by zinc-mediated reduction of a modified version[3]) of the *Baylis–Hillman* adduct in four steps. The asymmetric synthesis [5c] of pheromone **1** in six steps starting from (2*S*)-2-methylbutanal has been reported, but the overall yield was low. Moreover, generation of the (*E*)-configuration of the C=C bond and the methylation at the 2-position were associated with a number of by-products [5c]. Being aware of the potential of our methodology [9], we planned a one-pot two-step synthesis of compound **1** directly from an unmodified *Baylis–Hillman* adduct[4]) [19], which would compare favorably with the previously reported multistep transformations [4a,b][5b,c][6d] and rather tedious experimental protocols and complex reagents [5b,c][6d].

---

[3]) A number of methodologies have been developed for the reduction of acetyl and allyl bromide derivatives (modified versions) of *Baylis–Hillman* adducts [14b][15b,c].

[4]) The conversion of unmodified *Baylis–Hillman* adducts is more convenient and represents an atom economy as compared to that of modified adducts.

Considerable efforts have been reported for the synthesis of (±)-**2** [4a,b] [5b] [20] as well as of chiral (+)-manicone (**2**) [5c] [21], but only one synthesis of (+)-normanicone (**3**) is known [21b]. However, in most of these syntheses, the control of the two configurational factors, *i.e.*, (2*E*,4*S*) required multistep sequences [5c] [21] with low overall yields [5c] [21b] or resulted in moderate optical purity [21a].

In this report, starting from (2*S*)-2-methylbutanal (obtained in [5c] after six steps), we describe a three-step synthesis of (2*E*,4*S*)-2,4-dimethylhex-2-enoic acid (**1**) and a five-step common synthesis route (*via* **1**) of both (+)-(*S*)-manicone (**2**) and (+)-(*S*)-normanicone (**3**) (*Scheme 2*). Similarly, (+)-dominicalure-I (**6**) and (+)-dominicalure-II (**7**) were also efficiently synthesized with entire (*E*)-selectivity, high overall yields, and optical purity (*Scheme 3*). Thus, we explored the *Baylis–Hillman* adduct as a powerful intermediate for the synthesis of a series of pheromones. The latter could be employed as naturally occurring biological attractants, thus avoiding to resort to large amounts of contact insecticides and fumigants as well as avoiding the environmental problems associated with the use of the latter [22] [23].

Results and Discussion. – For the synthesis of pheromones **1**–**3** according to our protocol [9], the *Baylis–Hillman* adduct **4** was needed (*Scheme 2*). Starting from (2*S*)-2-methylbutanal [5c], *Fernandes et al*. have applied a number of reported methods to accelerate the transformation to **4** [6d] and to enhance its yield, but they failed. Moreover, a prolonged (20 days) exposure of the optically active aldehyde to a large excess of base like 1,4-diazabicylo[2.2.2]octane (DABCO; 2–3 equiv.) caused racemization of the aldehyde[5]) [6d] [24]. To overcome this problem, we followed the recently reported protocol for the asymmetric *Baylis–Hillman* reaction of α-branched chiral aldehydes in presence of 50 mol-% of DABCO in CH_2Cl_2 at room temperature [25]. With this protocol, we achieved a 51% yield of adduct **4**, isolated as an inseparable mixture of two diastereoisomers after 22 h. To enhance the yield of **4** without impairing the optical activity, we made several attempts to synthesize **4** within shorter time, based on methods published in a thorough literature survey [14b]. We thus established that the key factors for an improvement of the yield of **4** within hours without hampering the optical activity are a lower temperature (0°) [26], an excess of methyl acrylate (= methyl prop-2-enoate; 3 equiv.)[6]) [27a], and a moderate amount of DABCO (50–100 mol-%) [27]. Moreover, self-aldolization of the starting α-branched aldehydes [26] is suppressed at 0°. Indeed, under such optimized conditions, **4** was obtained in 71% yield as *syn*/*anti* diastereoisomers mixture in 2.3 : 1 after 20 h. The configuration of the products was assigned by the ^{1}H-NMR shifts and coupling constants of H–C(3) and H–C(4) [28].

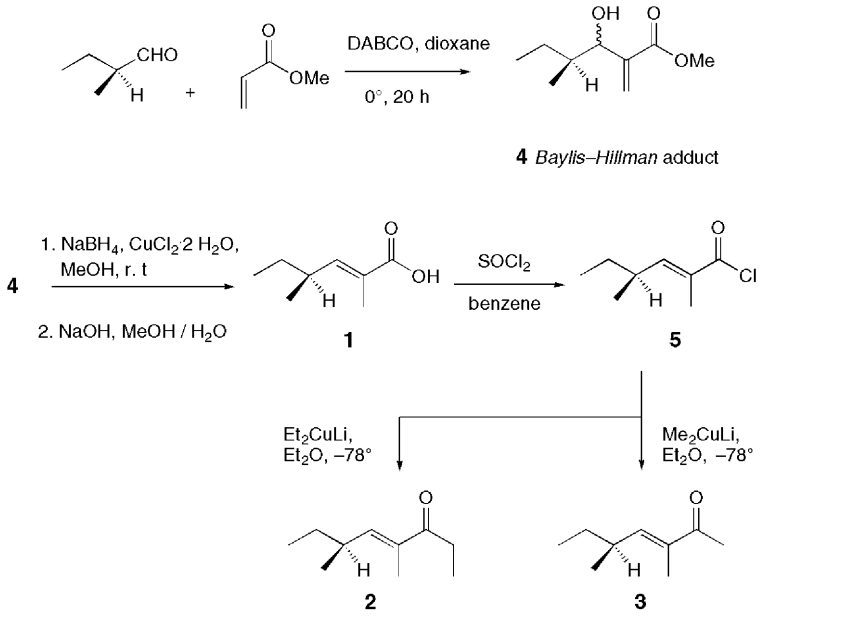
The *Baylis–Hillman* adducts **8a** (R = Et) and **8b** (R = ^{i}Pr) were prepared in 83 and 78% yield by treatment of propanal and 2-methylpropanal, respectively, with methyl acrylate (3 equiv.) in the presence of 100 mol-% DABCO in dioxane/water 1 : 1, according to the procedure described in the literature [14b] [27a] (*Scheme 3*).

---

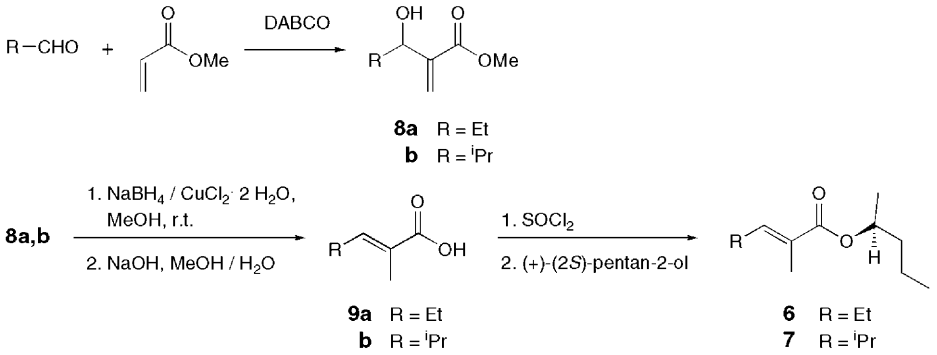
[5]) Racemization of chiral aldehydes on prolonged exposure to DABCO has been reported earlier [24].

[6]) The option of using an excess of acrylate in the *Baylis–Hillman* reaction reported in [25] was not possible since the reaction was intramolecular.

Scheme 2. *Synthesis of Pheromones* **1**–**3**



Scheme 3. *Synthesis of Pheromones* **6** *and* **7**



Following our reported method [9], the *Baylis–Hillman* adducts **4**, **8a**, and **8b** were then treated with $NaBH_4$ in the presence of $CuCl_2 \cdot 2H_2O$[7]) in MeOH, and the intermediate methyl (2*E*)-2-methylalk-2-enoates, present in a slightly alkaline medium after reduction, were hydrolyzed by 10% NaOH in MeOH in the same reaction vessel[8]) to afford, after workup, **1**, **9a**, and **9b** in 78, 76, and 75% yield, respectively (*Schemes 2*

[7]) A comparable result could be obtained by using CuCl in the same proportions.

[8]) Such a one-pot procedure for the reduction/alkaline hydrolysis was not applicable to the transformation described in [6d] due to the highly acidic reduction conditions.

and *3*). No attempt was made to separate the diastereoisomers of **4** since the reduction removed the stereogenic center at C(3).

The pheromone (2*E*,4*S*)-2,4-dimethylhex-2-enoic acid (**1**) was then converted to the corresponding acid chloride **5** with thionyl chloride. Treatment of **5** with lithium diethylcuprate or lithium dimethylcuprate in Et_2O solution at $-78°$ gave the desired compounds (+)-(*S*)-manicone (**2**) and (+)-(*S*)-normanicone (**3**) in 85 and 82% isolated yield, respectively (*Scheme 2*). On the other hand, the 2-methylalk-2-enoic acids **9a** and **9b** were esterified with (+)-(2*S*)-pentan-2-ol to furnish the two other target molecules **6** and **7**, respectively, with high overall yields and optical purity (*Scheme 3*).

In conclusion, we successfully applied the potential of *Baylis–Hillman* chemistry to the synthesis of five pheromones in high overall yield and optical purity, *i.e.*, of (2*E*,4*S*)-2,4-dimethylhex-2-enoic acid (**1**), (+)-(*S*)-manicone (**2**), (+)-(*S*)-normanicone (**3**), (+)-(1*S*)-1-methylbutyl (2*E*)-2-methylpent-2-enoate (=dominicalure-I; **6**) and (+)-(1*S*)-1-methylbutyl (2*E*)-2,4-dimethylpent-2-enoate (=dominicalure-II; **7**). Our straightforward strategy of deriving (2*E*)-2-methylalk-2-enoic acids from unmodified *Baylis–Hillman* adducts is simple, inexpensive, and perfectly stereoselective compared to the previous approaches. Optimized reaction conditions were developed for the preparation of the important optically active *Baylis–Hillmann* adduct **4**. The scope of this route can easily be extended to the synthesis of other related bioactive molecules.

The authors thank *UGC* and *CSIR*, New Delhi, for financial assistance.

Experimental Part

1. *General.* The *Baylis–Hillman* adducts **8a** and **8b** were prepared according to [27a]. (+)-(2*S*)-pentan-2-ol was purchased from *Lancaster Chemicals Company.* CC=Column chromatography; FC=flash chromatography. Optical rotations: *Jasco P-1020* polarimeter. IR Spectra: *Perkin-Elmer-1310* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian Gemini* 200 MHz (^1H) and *Bruker-UXNMR* 75 MHz (^{13}C); δ in ppm, *J* in Hz. LC-MS: *Agilent-1100-LC/MSD Trap SL* in the pos. mode; in *m*/*z*. Elemental analyses: *Perkin-Elmer-240C-CHN* analyzer.

2. Baylis–Hillman *Adducts. Methyl (3*R,*4*S*)- and (3*S,*4*R*)-3-Hydroxy-4-methyl-2-methylenehexanoate* (**4**). A soln. of (2*S*)-2-methylbutanal ($[\alpha]_D^{24}=+34.81$ ([5c]: $[\alpha]_D^{24}=+34.33$ (neat)); 2.16 ml, 20 mmol) and methyl acrylate (5.36 ml, 60 mmol) in dioxane (20 ml) was cooled to 0° in an ice bath, and DABCO (1.12 g, 10 mmol, 50 mol-%) was added. After completion of the reaction (20 h; TLC monitoring), ^{t}BuOMe (150 ml) and 5% aq. HCl soln. (50 ml) were added. The aq. phase was extracted with Et_2O (2×50 ml), the combined org. phase dried (Na_2SO_4), and evaporated, and the resulting residue purified by CC (5% AcOEt/hexane): **4** (2.44 g, 71%) as an inseparable *syn*/*anti* mixture 2.3:1. Colorless oil. IR (KBr): 3485, 2965, 2932, 2880, 1726, 1631. ^1H-NMR (200 MHz, $CDCl_3$): 0.80–0.96 (*m*, 6 H); 1.09–1.21 (*m*, 1.4 H, *syn*); 1.35–1.51 (*m*, 0.6 H, *anti*); 1.59–1.76 (*m*, 1 H); 2.60 (*d*, *J*=6.5, 0.7 H, *syn*); 2.83 (*d*, *J*=8.0, 0.3 H, *anti*); 3.76 (*s*, 3 H); 4.08 (*t*, *J*=8.0, 0.3 H, *anti*); 4.30 (*t*, *J*=6.5, 0.7 H, *syn*); 5.74 (*s*, 0.3 H, *anti*); 5.79 (*s*, 0.7 H, *syn*); 6.24 (*s*, 0.3 H, *anti*); 6.27 (*s*, 0.7 H, *syn*). ^{13}C-NMR (75 MHz, $CDCl_3$): *syn* isomer: 11.9; 13.4; 26.8; 39.0; 52.0; 74.7; 125.6; 142.3; 167.3; *anti* isomer: 11.5; 16.0; 24.5; 39.5; 52.0; 76.8; 126.3; 141.9; 167.5. LC-MS: 173 ($[M+1]^+$). Anal. calc. for $C_9H_{16}O_3$: C 62.79, H 9.30; found: C 62.70, H 9.34.

Methyl 3-Hydroxy-2-methylenepentanoate (**8a**). A soln. of propanal (1.45 ml, 20 mmol) and methyl acrylate (5.36 ml, 60 mmol) in dioxane/H_2O 1:1 (50 ml) was stirred at r.t. in the presence of DABCO (100 mol-%, 2.24 g, 20 mmol). Upon completion of the reaction (TLC monitoring), ^{t}BuOMe (500 ml) and H_2O (150 ml) were added. The org. phase was washed with brine (2×80 ml), dried (Na_2SO_4), and evaporated, and the resulting residue purified by CC (4% AcOEt/hexane): **8a** (2.39 g, 83%). Colorless

oil. IR (KBr): 3438, 2967, 2880, 1715, 1630, 1440. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.92 (*t*, *J* = 7.0, 3 H); 1.51–1.73 (*m*, 2 H); 3.08 (br., 1 H); 3.75 (*s*, 3 H); 4.32 (*t*, *J* = 7.0, 1 H); 5.81 (*s*, 1 H); 6.20 (*s*, 1 H). LC-MS: 145 ($[M+1]^+$). Anal. calc. for $C_7H_{12}O_3$: C 58.33, H 8.33; found: C 58.42, H 8.28.

Methyl 3-Hydroxy-4-methyl-2-methylenepentanoate (**8b**). As described for **8a**, from 2-methylpropanal (1.81 ml, 20 mmol): **8b** (2.46 g, 78%). Colorless oil. IR (KBr): 3525, 2959, 2875, 1726, 1630, 1440. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.88 (*d*, *J* = 7.0, 3 H); 0.93 (*d*, *J* = 7.0, 3 H); 1.82–1.98 (*m*, 1 H); 2.32 (br., 1 H); 3.77 (*s*, 3 H); 4.04 (*d*, *J* = 7.0, 1 H); 5.75 (*s*, 1 H); 6.22 (*s*, 1 H). LC-MS: 159 ($[M+1]^+$). Anal. calc. for $C_8H_{14}O_3$: C 60.76, H 8.86; found: C 60.68, H 8.93.

3. *One-pot Preparation of (2*E*)-2-Methylalk-2-enoic Acids: General Procedure* [9]. The *Baylis–Hillman* adduct (10 mmol) and $CuCl_2 \cdot 2H_2O$ (2.56 g, 15 mmol) were dissolved in MeOH (30 ml), and the mixture was stirred for 10 min at 0°. $NaBH_4$ (0.58 g, 15 mmol) was added in portions with stirring (vigorous gas evolution). Stirring was continued for 30 min until gas evolution ceased. To the resulting slightly alkaline soln., 40% NaOH/MeOH (10 ml) was added dropwise while cooling in an ice bath and maintaing an overall alkali concentration of 10%. Then the mixture was stirred for 12 h at 25°. After the addition of H_2O (80 ml), the mixture was washed with Et_2O (2 × 50 ml). Then the aq. phase was acidified to pH 2 with 10% HCl soln. and extracted with Et_2O (3 × 50 ml). The extract was washed with brine, dried (Na_2SO_4), and evaporated: (2*E*)-2-methylalk-2-enoic acid.

(*2*E,*4*S*)-2,4-Dimethylhex-2-enoic Acid* (**1**): Yield 1.1 g (78% from **4**). Colorless oil. $[\alpha]_D^{24} = +35.13$ ($c = 2.696$, benzene) ([29]: $[\alpha]_D^{24} = +34.6$ ($c = 2.65$, benzene)). IR (KBr): 3419, 2964, 2927, 2875, 1688, 1640. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.88 (*t*, *J* = 7.0, 3 H); 1.03 (*d*, *J* = 7.0, 3 H); 1.35–1.44 (*m*, 2 H); 1.85 (*d*, *J* = 1.5, 3 H); 2.40–2.49 (*m*, 1 H); 6.71 (*dd*, *J* = 10.0, 1.5, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.9; 12.5; 18.0; 29.0; 33.8; 125.2; 149.5; 173.6. LC-MS: 143 ($[M+1]^+$). Anal. calc. for $C_8H_{14}O_2$: C 67.60, H 9.86; found: C 67.71, H 9.79.

*(2*E*)-2-Methylpent-2-enoic Acid* (**9a**): Yield 0.866 g (76% from **8a**). Colorless oil. IR (KBr): 3450, 2929, 1690, 1639. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.20 (*t*, *J* = 7.0, 3 H); 1.80 (*s*, 3 H); 2.14–2.33 (*m*, 2 H); 6.88 (*t*, *J* = 7.0, 1 H); 11.6 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.9; 13.0; 22.4; 126.9; 146.8; 174.4. LC-MS: 115 ($[M+1]^+$). Anal. calc. for $C_6H_{10}O_2$: C 63.15, H 8.77; found: C 63.24, H 8.88.

*(2*E*)-2,4-Dimethylpent-2-enoic Acid* (**9b**): Yield 0.958 g (75% from **8b**). Colorless oil. IR (KBr): 3417, 2925, 1696, 1618. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.08 (*d*, *J* = 7.0, 6 H); 1.81 (*d*, *J* = 1.5, 3 H); 2.59–2.78 (*m*, 1 H); 6.74 (*dd*, *J* = 10.5, 1.5, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.8; 21.9; 26.0; 125.2; 151.6; 174.3. LC-MS: 129 ($[M+1]^+$). Anal. calc. for $C_7H_{12}O_2$: C 65.62, H 9.37; found: C 65.54, H 9.42.

4. *(2*E,*4*S*)-2,4-Dimethylhex-2-enoyl Chloride* (**5**). A soln. of **1** (1 g, 7 mmol) in benzene (10 ml) was added to a stirred soln. of $SOCl_2$ (2.12 g, 18 mmol) in benzene (10 ml), and the resulting mixture was refluxed for 2 h, then cooled, and evaporated: crude **5** (1.127 g, 100%) which was used in the next step without further purification.

5. *(4*E,*6*S*)-4,6-Dimethyloct-4-en-3-one* (**2**). A 1.56M EtLi soln. in Et_2O (7.7 ml, 12 mmol) was added to a stirred suspension of CuI (1.14 g, 6 mmol) and Et_2O (10 ml) cooled to −40°. After stirring for 15 min, the mixture was cooled to −78° and a soln. of **5** (560 mg, 3.5 mmol) in Et_2O (5 ml) was dropwise added. After stirring for 15 min at −78°, MeOH (5 ml) was added, and the mixture was allowed to warm to r.t., then poured into a large excess of sat. aq. NH_4Cl soln., and extracted with Et_2O. The org. extract was washed with aq. NH_4Cl soln., dried, and evaporated and the residue purified by FC (silica gel, 7% AcOEt/hexane): **2** as (458 mg, 85%). Colorless oil. $[\alpha]_D^{24} = +44.11$ ($c = 4.86$, Et_2O) ([21b]: $[\alpha]_D^{24} = +43.8$ ($c = 5$, Et_2O)). IR (KBr): 1672, 1640, 1460. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.87 (*t*, *J* = 7.5, 3 H); 1.02 (*d*, *J* = 6.4, 3 H); 1.10 (*t*, *J* = 7.3, 3 H); 1.26–1.51 (*m*, 2 H); 1.79 (*d*, *J* = 1.5, 3 H); 2.43–2.52 (*m*, 1 H); 2.69 (*q*, *J* = 7.3, 2 H); 6.38 (*dd*, *J* = 1.5, 9.8, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 8.9; 11.3; 12.0; 19.9; 29.5; 29.9; 35.5; 135.8; 147.8; 202.9. LC-MS: 155 ($[M+1]^+$). Anal. calc. for $C_{10}H_{18}O$: C 77.92, H 11.68; found: C 77.81, H 11.59.

*(3*E,*5*S*)-3,5-Dimethylhept-3-en-2-one* (**3**). As described for **2**, with 1.6M MeLi soln. in Et_2O (7.5 ml, 12 mmol), CuI (1.14 g, 6 mmol) in Et_2O, and **5** (560 mg, 3.5 mmol) in Et_2O: **3** (402 mg, 82%). Colorless oil. $[\alpha]_D^{24} = +38.09$ ($c = 4.24$, Et_2O) ([21b]: $[\alpha]_D^{24} = +37.60$ ($c = 5$, Et_2O)). IR (KBr): 1686, 1638, 1461. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.88 (*t*, *J* = 7.5, 3 H); 1.03 (*d*, *J* = 6.4, 3 H); 1.25–1.50 (*m*, 2 H); 1.77 (*d*, *J* = 1.5, 3 H);

2.29 (*s*, 3 H); 2.42–2.51 (*m*, 1 H); 6.32 (*dd*, *J* = 1.5, 9.8, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.6; 12.1; 20.2; 25.8; 30.0; 35.8; 136.7; 149.3; 200.0. LC-MS: 141 ($[M+1]^+$). Anal. calc. for $C_9H_{16}O$: C 77.14, H 11.43; found: C 77.23, H 11.47.

6. *Esterification of (2*E*)-2-Methylalk-2-enoic Acids: General Procedure.* A mixture of (2*E*)-2-methylalk-2-enoic acid (2 mmol) and thionyl chloride (354 mg, 3 mmol) was refluxed for 30 min. The excess thionyl chloride was evaporated and the residual acid chloride treated with (+)-(2*S*)-pentan-2-ol (3 mmol) at 50° for 30 min. The mixture was diluted with Et_2O (50 ml), washed with brine (3×10 ml), dried, and evaporated and the crude oil subjected CC: ester.

*(+)-(1*S*)-1-Methylbutyl (2*E*)-2-Methylpent-2-enoate* (**6**): 0.250 g (68%). Colorless oil. $[\alpha]_D^{24} = +13.9$ ($c = 1.173$, Et_2O) ([13]: $[\alpha]_D^{24} = +13.4$ ($c = 0.175$, Et_2O)). IR (KBr): 2964, 1709, 1618. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.5, 3 H); 1.06 (*t*, *J* = 7.0, 3 H); 1.22 (*d*, *J* = 7.0, 3 H); 1.28–1.63 (*m*, 4 H); 1.80 (*d*, *J* = 1.6, 3 H); 2.07–2.22 (*m*, 2 H); 4.82–4.98 (*m*, 1 H); 6.65 (*dt*, *J* = 7.0, 1.6, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 12.8; 13.7; 17.1; 18.6; 19.9; 22.1; 36.0; 70.1; 127.8; 143.2; 167.9. LC-MS: 185 ($[M+1]^+$). Anal. calc. for $C_{11}H_{20}O_2$: C 71.74, H 10.87; found: C 71.66, H 10.77.

*(+)-(1*S*)-1-Methylbutyl (2*E*)-2,4-Dimethylpent-2-enoate* (**7**): 0.273 g (69%). Colorless oil. $[\alpha]_D^{24} = +11.4$ ($c = 1.632$, Et_2O) ([13]: $[\alpha]_D^{24} = +10.9$ ($c = 1.256$, Et_2O)). IR (KBr): 2926, 2855, 1736. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.91 (*t*, *J* = 7.0, 3 H); 1.05 (*d*, *J* = 7.0, 6 H); 1.09 (*d*, *J* = 7.0, 3 H); 1.22–1.40 (*m*, 4 H); 1.83 (*d*, *J* = 1.5, 3 H); 2.58–2.64 (*m*, 1 H); 4.84–4.96 (*m*, 1 H); 6.48 (*dd*, *J* = 10.5, 1.5, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.9; 18.8; 19.2; 20.5; 21.5; 22.2; 38.1; 70.8; 126.1; 148.3; 168.2. LC-MS: 199 ($[M+1]^+$). Anal. calc. for $C_{12}H_{22}O_2$: C 72.73, H 11.11; found: C 72.79, H 11.23.

REFERENCES

[1] J. W. S. Bradshaw, R. Baker, P. E. Howse, *Nature* (*London*) **1975**, *258*, 230; M. J. Garson, *Chem. Rev.* **1993**, *93*, 1699; M. A. D'Auria, L. Minale, R. Riccio, *Chem. Rev.* **1993**, *93*, 1839.

[2] A. Marfat, P. R. McGuirk, P. Helquist, *J. Org. Chem.* **1979**, *44*, 3888.

[3] Y. Masaki, K. Sakuma, K. Kaji, *J. Chem. Soc., Chem. Commun.* **1980**, 434; H. C. Brown, D. Basavaiah, *J. Org. Chem.* **1982**, *47*, 5407; S. E. Denmark, J. Amburgey, *J. Am. Chem. Soc.* **1993**, *115*, 10386; L. Navarre, S. Darses, J. P. Genet, *J. Chem. Soc., Chem. Commun.* **2004**, 1108; H. Amri, M. Rambaud, J. Villieras, *Tetrahedron* **1990**, *46*, 3535.

[4] a) J. A. Katzenellenbogen, T. Utawanit, *J. Am. Chem. Soc.* **1974**, *96*, 6153; b) P. J. Kocienski, J. N. Ansell, R. W. Ostrow, *J. Org. Chem.* **1976**, *41*, 3625; c) J. A. Miller, G. Zweifel, *J. Am. Chem. Soc.* **1981**, *103*, 6217.

[5] a) R. Rossi, A. Carpita, T. Messeri, *Synth. Commun.* **1992**, *22*, 603; b) P. Coutrot, A. Ghribi, *Synthesis* **1986**, 790; c) R. Rossi, A. Carpita, P. Cossi, *Tetrahedron* **1992**, *48*, 8801.

[6] a) D. Basavaiah, M. Krishnamacharyulu, R. S. Hyma, P. K. S. Sarma, N. Kumaragurabaran, *J. Org. Chem.* **1999**, *64*, 1197; b) U. Shadakshari, S. K. Nayak, *Tetrahedron* **2001**, *57*, 4599; c) J. Li, W. Qian, Y. Zhang, *Tetrahedron* **2004**, *60*, 5793; d) L. Fernandes, A. J. Bortoluzzi, M. M. Sa', *Tetrahedron* **2004**, *60*, 9983.

[7] B. Das, J. Banerjee, N. Ravindranath, B. Venkataiah, *Tetrahedron Lett.* **2004**, *45*, 2425; B. Das, J. Banerjee, N. Ravindranath, *Tetrahedron* **2004**, *60*, 8357.

[8] B. Das, J. Banerjee, G. Mahender, A. Majhi, *Org. Lett.* **2004**, *6*, 3349; B. Das, G. Mahender, N. Chowdhury, J. Banerjee, *Synlett* **2005**, 1000.

[9] B. Das, J. Banerjee, A. Majhi, G. Mahender, *Tetrahedron Lett.* **2004**, *45*, 9225.

[10] J. M. Brand, R. M. Duffield, J. G. MacConnell, M. S. Blum, H. M. False, *Science* (*Washington, D.C.*) **1973**, *179*, 388.

[11] H. M. Fales, M. S. Blum, R. M. Crewe, J. M. Brand, *J. Insect. Physiol.* **1972**, *18*, 1077.

[12] H. J. Bestmann, A. B. Attygalle, J. Glasbrenner, R. Riemer, O. Vostrowsky, *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 784.

[13] H. J. William, R. M. Silverstein, W. E. Burkholder, A. Khorramshahi, *J. Chem. Ecol.* **1981**, *7*, 759; L. Lin-Yu, L. Guo-Qiang, *J. Chem. Ecol.* **1990**, *16*, 1921.

[14] a) A. B. Baylis, M. E. D. Hillman, German Patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q; b) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811 and ref. cit. therein.

[15] a) H. M. R. Hoffmann, J. Rabe, *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94; b) H. M. R. Hoffmann, J. Rabe, *J. Org. Chem.* **1985**, *50*, 3849; c) D. Basavaiah, N. Kumaragurubaran, *Tetrahedron Lett*. **2001**, *42*, 477; d) S. E. Drewes, N. D. Emslie, *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079.
[16] W. R. Roush, B. B. Brown, *J. Org. Chem.* **1993**, *58*, 2151; T. Jenn, D. Heissler, *Tetrahedron* **1998**, *54*, 97.
[17] D. Grassi, V. Lippuner, M. Aebi, J. Brunner, A. Vasella, *J. Am. Chem. Soc.* **1997**, *119*, 10992.
[18] C. R. Mateus, M. P. Feltrin, A. M. Costa, F. Cohello, W. P. Almedia, *Tetrahedron* **2001**, *57*, 6901; D. Basavaiah, R. S. Hyma, *Tetrahedron* **1996**, *52*, 1253.
[19] B. M. Trost, *Science* (*Washington, D.C.*) **1991**, *254*, 1471.
[20] A. Alexakis, A. Commercon, C. Coulentianos, J. F. Normant, *Tetrahedron* **1964**, *40*, 715; R. Yoneda, S. Harusawa, T. Kurihara, *J. Chem. Soc., Perkin Trans. 1* **1988**, 3163.
[21] a) T. Mimura, Y. Kimura, T. Nakai, *Chem. Lett*. **1979**, 1361; b) V. Martischonok, G. G. Melikyan, A. Mineif, O. Vostrowsky, H. J. Bestmann, *Synthesis* **1991**, 560; c) N. De Kimpe, W. Aelterman, *Tetrahedron* **1996**, *52*, 12815.
[22] H. A. U. Monro, E. Upitis, E. J. Bond, *J. Stored Prod. Res.* **1972**, *8*, 199.
[23] C. J. Lloyd, *J. Stored Prod. Res.* **1973**, *9*, 77.
[24] S. E. Drews, A. A. Khan, K. Rowland, *Synth. Commun.* **1993**, 2*3*, 183.
[25] P. Radhakrishna, V. Kannan, G. V. M. Sharma, *J. Org. Chem.* **2004**, *69*, 6467.
[26] S. Rafel, J. W. Leahy, *J. Org. Chem.* **1997**, *62*, 1521.
[27] a) C. Yu, B. Liu, L. Hu, *J. Org. Chem.* **2001**, *66*, 5413; b) P. Radhakrishna, A. Manjuvani, E. Raja Sekhar, *ARKIVOC* **2005**, III, 99.
[28] C. H. HeathCock, in 'Asymmetric Synthesis', Vol. 3, Ed. J. D. Morrison, Academic Press, Orlando, 1984, p. 111–118.
[29] N. Slogui, G. Rousseau, J. M. Conia, *Synthesis* **1982**, 58.

Received December 29, 2005