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Practical Stereoselective Synthesis of (2*E*)- and (2*Z*)-4-Cycloalkylidenebut-2-enoic Acids

Stoyan K. Karagiozov and Frank S. Abbott*

Division of Biomolecular and Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C., Canada

ABSTRACT

Stereoselective synthesis of α,β-unsaturated esters **7** and **8** was achieved through Horner–Wadsworth–Emmons reaction of β,β-disubstituted α,β-unsaturated aldehydes. Thus, aldehydes **6** undergo olefination with phosphonate carbanion generated from triethyl phosphonoacetate **3** and lithium hydroxide or butyl lithium/DMPU to give (*E*)-α,β-unsaturated esters **7** with excellent selectivity. The treatment of **6** with the new Horner–Emmons reagents, ethyl(diphenylphosphono)acetate **4a** and ethyl (di-o-tolyl-phosphono) acetate **4b** in the presence of benzyltrimethyl ammonium hydroxide (Triton B) afforded (*Z*)-α,β-unsaturated

*Correspondence: Frank S. Abbott, Division of Biomolecular and Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver V6T 1Z3, B.C., Canada; Fax: +(604) 822-3035; E-mail: fabbott@interchange.ubc.ca.

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esters **8** with 73–89% selectivity. The esters **7** and **8** were converted to (2*E*)- and (2*Z*)-4-cycloalkylidenebut-2-enoic acids **9** and **10**, respectively.

Key Words: Wittig reactions; Phosphonate carbanions; Stereoselective synthesis; α,β-Unsaturated esters; Carboxylic acids.

Synthesis of carbon–carbon double bonds with a high degree of selectivity is of great interest in synthetic organic chemistry and is of significant value in preparing olefins that exhibit biological properties that are strongly dependent upon stereochemistry. The Wittig reaction and its modification, the base-promoted Horner–Wadsworth–Emmons olefination of aldehydes and ketones with phosphonate carbanions, is a widely employed approach to the synthesis of α,β-unsaturated esters.[1] In view of our interest in the design of selected substituted (2*E*)- and (2*Z*)-4-substituted but-2-enoic acids that could represent a new class of antiepileptic candidates, our strategy was based on the coupling of the β,β-disubstituted α,β-unsaturated aldehydes **6** and the generated phosphonate carbanions under specific conditions that provide high *E*- and *Z*-stereoselectivity (Sch. 1). The starting compounds **6** were obtained by olefination of ketones **1** with diethyl cyanomethyl phosphonate **2** carried out in ether or DMF to provide nitriles **5**.[2a] Further reduction with DIBALH carried out in pentane or ether, gave known aldehydes **6a–c**[2b] (Sch. 1). Reduction of nitrile **5d**, performed in pentane or ether afforded aldehyde **6d** in 47% and 56% yield, respectively, when purified by flash chromatography. Attempts to isolate **6d** by vacuum distillation resulted in the formation of a mixture of **6d** and **6e** due to isomerization. The ^{1}H NMR spectrum of the distilled mixture indicated that the ratio of products formed was approximately 1 : 1. Aldehyde **6d** exhibited two doublets at $\delta = 9.96$ and 5.84 due to CHO and CH═C protons, respectively. The presence of two triplets at $\delta = 9.46$ (CHO) and 5.29 (CH═C) for one proton each were assigned for the enal **6e**. Further purification by chromatotron chromatography afforded pure **6d** (Sch. 2).

Initially the stereoselective conversion of aldehydes **6** to (*E*)-α,β-unsaturated esters **7** was performed under $LiOH \cdot H_2O$-promoted Horner–Wadsworth–Emmons conditions with triethyl phosphonoacetate **3**.[3,4] When aldehydes **6** were allowed to react with **3** in the presence of $LiOH \cdot H_2O$ (1.1 equiv)[4] for 2.5–16 hr the target (*E*)-α,β-unsaturated esters **7** were obtained mainly as a single product with high (*E*)-selectivity (93–98%) in 38–64% yields (entries 2, 5, 8, and 11, Table 1) and only a small amount of the corresponding *Z*-esters **8** were isolated. The yields were slightly increased to 41–66% when the reaction time was reduced to 2.5 hr (entries 4, 7, 10) except for **7a** where the yield was increased from 38% to 65% (entry 1). These results

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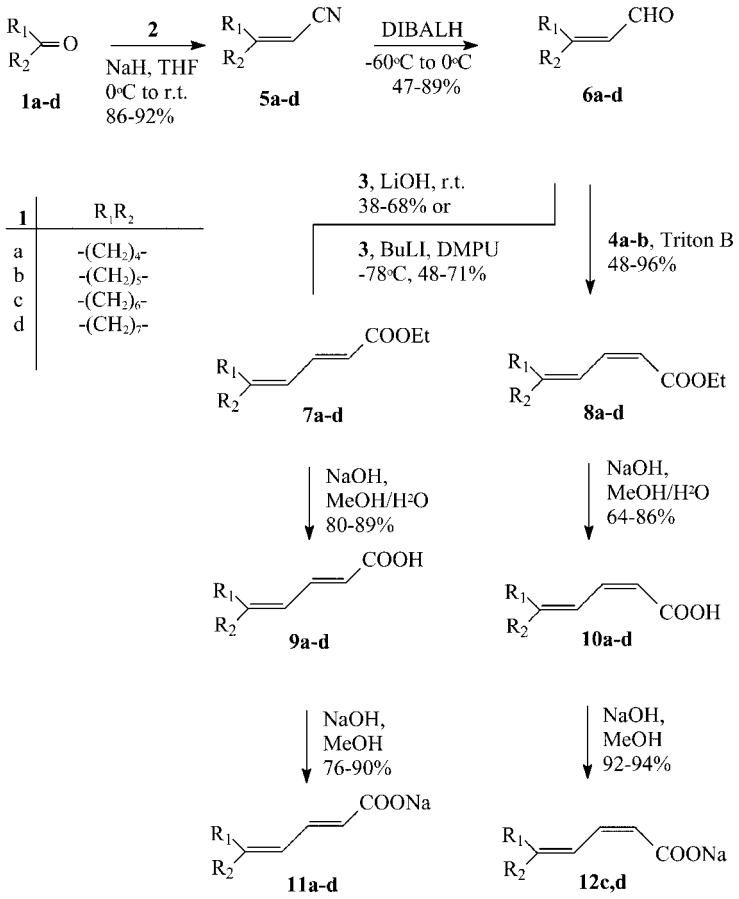
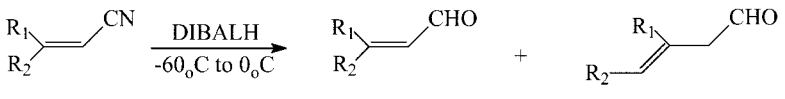


Scheme 1. Synthesis of (2*E*)- and (2*Z*)-4-cycloalkylidenebut-2-enoic acids.

confirmed that despite an excess of base the competing ester hydrolysis occurred at a very slow rate.[3] An alternative method was applied as reagent **3** was treated with BuLi (1.8 equiv) and DMPU (3.6 equiv) in THF at 0°C,



Scheme 2. Reduction of nitrile **5d** with DIBALH.

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Table 1. Horner–Wadsworth–Emmons reaction of $R^1R^2C{=}CHCHO$ **6** with $(EtO)_2P(O)CH_2COOEt$ **3** in THF.

Entry	**6**	R^1R^2	Base	Reaction conditions	Yield **7** (%)	(*E*/*Z*)
1	**a**	$-(CH_2)_4-$	$LiOH \cdot H_2O$	r.t., 2.5 hr	65	98 : 2
2	**a**	$-(CH_2)_4-$	$LiOH \cdot H_2O$	r.t., 16 hr	38	98 : 2
3	**a**	$-(CH_2)_4-$	BuLi, DMPU	−78°C to 0°C, 3.5 hr	50	>99
4	**b**	$-(CH_2)_5-$	$LiOH \cdot H_2O$	r.t., 2.5 hr	66	93 : 7
5	**b**	$-(CH_2)_5-$	$LiOH \cdot H_2O$	r.t., 16 hr	64	93 : 7
6	**b**	$-(CH_2)_5-$	BuLi, DMPU	−78°C to 0°C, 3.5 hr	71	97 : 3
7	**c**	$-(CH_2)_6-$	$LiOH \cdot H_2O$	r.t., 2.5 hr	41	96 : 4
8	**c**	$-(CH_2)_6-$	$LiOH \cdot H_2O$	r.t., 16 hr	40	96 : 4
9	**c**	$-(CH_2)_6-$	BuLi, DMPU	−78°C to 0°C, 3.5 hr	64	98 : 2
10	**d**	$-(CH_2)_7-$	$LiOH \cdot H_2O$	r.t., 2.5 hr	58	96 : 4
11	**d**	$-(CH_2)_7-$	$LiOH \cdot H_2O$	r.t., 16 hr	48	96 : 4
12	**d**	$-(CH_2)_7-$	BuLi, DMPU	−78°C to 0°C, 3.5 hr	70	98 : 2

followed by **6** at −78°C and warming to 0°C over 1.5 hr to give esters **7** with *E*-stereoselectivity (97–99%) in 50–71% yields (entries 3, 6, 9, and 12, Table 1). Finally, esters **7** were cleanly hydrolyzed under basic conditions[5] to (*E*)-acids **9** in 60–89% yield. (*E*)-acids **9** were converted to sodium salts **11** with NaOH in MeOH. The stereochemistry of the 2,3 double bond in **7–11** was determined on the basis of the coupling constants of vinyl proton signals in the ^1H NMR spectra.

The next focus was on the stereoselective synthesis of (2*Z*)-4-cycloalkylidenebut-2-enoates **8**. Since Wittig and other related reactions such as Horner–Emmons modification preferentially give the more stable (*E*)-unsaturated isomers, we reviewed the latest findings devoted to the construction of (*Z*)-α,β-unsaturated esters.[6,7] The Horner–Wadsworth–Emmons olefination was performed on aldehydes **6** with ethyl (diphenylphosphono)acetate **4a** and ethyl (di-*o*-tolylphosphono) acetate **4b**, respectively, in the presence of benzyltrimethylammonium hydroxide (40% in MeOH) (triton B) as a base in THF. When **6a,b** were treated with **4a** at −78°C for 1 hr followed by warming to 0°C over 3 hr the olefination occurred smoothly to give the corresponding (2*Z*)-4-cycloalkylidenebut-2-enoates **8a** and **8b** with (*Z*)-selectivity (73% and 75%) (entries 1 and 3, Table 2). Slightly improved Z-selectivity (78% and 79%) was obtained with **6c** and **6d** as partners in the reaction (entries 5, 8). Subsequently, we further studied the reaction with ethyl (di-*o*-tolylphosphono)acetate **4b** in an attempt to improve the (*Z*)-selectivity and yields. When **4b** was treated with triton B at −78°C for 15 min, stirred for 30 min, followed by **6** for 20 min and warming to 0°C over 6 hr, the

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Table 2. Horner–Wadsworth–Emmons reaction of $R^1R^2C{=}CHCHO$ **6** with $(o\text{-}R\text{-}Ar)_2P(O)CH_2CO_2Et$ **4** in THF in the presence of triton B.

Entry	**6**	R^1R^2	**4**	R	Reaction conditions	Yield **8** (%)	(*Z*/*E*)
1	**a**	$-(CH_2)_4-$	**a**	H	−78°C to −50°C 1 hr, −50°C to −20°C 1 hr −20°C to 0°C 1 hr	47	73 : 27
2	**a**	$-(CH_2)_4-$	**b**	Me	78°C to −25°C 1.5 hr 25°C to 0°C 1.5 hr	56	79 : 21
3	**b**	$-(CH_2)_5-$	**a**	H	−78°C to −50°C 1 hr −50°C to −20°C 1 hr −20°C to 0°C 1 hr	61	75 : 25
4	**b**	$-(CH_2)_5-$	**b**	Me	78°C to −25°C 1.5 hr 25°C to 0°C 1.5 hr	67	82 : 18
5	**c**	$-(CH_2)_6-$	**a**	H	−78°C to −50°C 1 hr −50°C to −20°C 1 hr −20°C to 0°C 1 hr	45	78 : 22
6	**c**	$-(CH_2)_6-$	**b**	Me	−78°C to −25°C 1.5 hr −25°C to 0°C 1.5 hr	76	89 : 11
7	**c**	$-(CH_2)_6-$	**b**	Me	−78°C 30 min −78°C to −35°C 2.5 hr −35°C to −15°C 1 hr −15°C to 0°C 2 hr	84	89 : 11
8	**d**	$-(CH_2)_7-$	**a**	H	−78°C to −50°C 1 hr −50°C to −20°C 1 hr −20°C to 0°C 1 hr	38	79 : 21
9	**d**	$-(CH_2)_7-$	**b**	Me	−78°C to −25°C 1.5 hr −25°C to 0°C 1.5 hr	66	85 : 15
10	**d**	$-(CH_2)_7-$	**b**	Me	−78°C 30 min −78°C to −35°C 2.5 hr −35°C to −15°C 1 hr −15°C to 0°C 2 hr	82	85 : 15

(*Z*)-selectivity was improved to 79–89% and the (2*Z*)-4-cycloalkylidenebut-2-enoates **8a–d** were obtained in 56–82% yield (entries 2, 4, 6, 10). The results indicated that the (*Z*)-selectivity and yield increased with increasing the size of the cycloalkyl substituent at the β,β-position of the α,β-unsaturated aldehydes **6**. The results are summarized in Table 2.

The *Z*/*E* ratios of all Horner–Wadsworth–Emmons products **8**/**7** were determined by integrating the vinyl proton signals in the 300 MHz ^{1}H NMR spectra of a mixed sample of both isomers purified by chromatotron and/or by analysis of the pure (*E*)- and (*Z*)-isomers isolated by further chromatography purification. The chromatography did not affect the *Z*/*E* ratio of the isomers.

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Further basic hydrolysis of **8** under mild conditions afforded the corresponding (2*Z*)-4-cycloalkylidenebut-2-enoic acids **10** in excellent yields. The selected (*Z*)-acids **10c,d** were converted to the corresponding sodium salts **12c,d** by treatment with NaOH in MeOH.

In summary, we reported the synthesis of (2*E*)- and (2*Z*)-4-cycloalkylidenebut-2-enoic acids that could represent a new class of antiepileptic candidates. We have demonstrated synthetic routes for the preparation of α,β-unsaturated esters with high (*E*)- and (*Z*)-stereoselectivity from β,β-disubstituted α,β-unsaturated aldehydes under the base-promoted Horner–Wadsworth–Emmons reaction utilizing a broad range of conditions. The LiOH-promoted Horner–Wadsworth–Emmons reaction with triethyl phosphonomethylacetate gave the corresponding (2*E*)-2,4-pentadienoates in 93–97% stereoselectivity and with moderate yields. Using BuLi/DMPU and an excess of phosphonate anion increased the yields while retaining the high *E*-selectivity. We have also extended the utilization of newer (*Z*)-selective Horner–Wadsworth–Emmons reagents recently discovered by Ando and coworkers such as ethyl (diphenylphosphono)acetate **4a** and ethyl (di-o-tolylphosphono)acetates **4b** for the preparation of (2Z)-4-cycloalkylidenebut-2-enoates, which were obtained in 73–89% (*Z*)-selectivity and with moderate to good yields. The methodologies employed could afford the preparation of building blocks with a variety of synthetic applications requiring conjugated double bonds with defined stereochemistry.

EXPERIMENTAL

All air and/or water sensitive reactions were performed in flasks flame dried under a positive flow of argon and conducted under Ar with, freshly distilled anhydrous solvents using standard syringe/cannula/septa techniques. THF and Et_2O were distilled from sodium/benzophenone. CH_2Cl_2 and pentane were dried over CaH_2 and distilled. The starting materials were synthesized as described in the literature with some modifications. ^{1}H NMR spectra were recorded on Bruker spectrometers Avance AV-300 (300 MHz), Avance AV-400 (400 MHz), Bruker AC-200 (200 MHz) and Bruker WH-400 (400 MHz) using the indicated solvents. Chemical shifts are expressed in ppm with TMS as internal standard. Data are reported as follows: chemical shift multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constants (Hz). ^{13}C NMR spectra were recorded on AV-300 (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as internal reference. IR spectra were obtained on a Perkin–Elmer 1600 FT instrument. Elemental analyses were performed on a Carlo Erba model 1106 CHN elemental

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analyzer, melting points were recorded on a Fisher–Johns apparatus and are uncorrected. LC-MS was recorded on a Fisons VG Quattro (Altrincham UK) tandem spectrometer with Hewlett Packard (Avondale PA) 1090II liquid chromatograph. HRMS were recorded on Kratos MS 50, MS-80 or Concept II HQ mass spectrometers. Analytical TLC was performed using silica gel 60 F254 precoated plates Merck, 0.25 mm thickness with a fluorescent indicator. Visualization was accomplished with one or more of the following: UV light (254 nm), $KMnO_4/5\%NaOH/K_2CO_3/H_2O$ (1 : 4 : 6.5 : 100) solution and heat as a developing agent. Flash column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm) using the indicated solvents. Chromatotron chromatography was performed on a 7924T Chromatotron, Harrison on silica gel, 60 PF-254 (with calcium sulfate), TLC grade 7749, E. Merck. Solvents were evaporated under reduced pressure using a Buchi rotary evaporator connected to a water aspirator. Chemicals were purchased from Acros, Aldrich, BDH, Fluka, and TCI and were used without further purification.

Cyclooctylideneacetonitrile (5d); Typical Procedure

To a stirred suspension of sodium hydride (1.48 g, 37.0 mmol, 60% in mineral oil) in anhyd DMF (50 mL) under argon at 0°C was added dropwise a solution of diethyl cyanomethylphosphonate **2** (6.7 g, 37.0 mmol) in DMF (15 mL) over 20 min. The stirring was continued for 60 min and cyclooctanone **1d** (4.24 g, 33.6 mmol) in DMF (15 mL) was added over 15 min and the reaction mixture allowed to warm to r.t. overnight. The reaction was quenched with H_2O (300 mL), extracted with Et_2O (5 × 50 mL), washed with H_2O (100 mL) and brine (100 mL), respectively, and dried over $MgSO_4$. The Et_2O was evaporated under reduced pressure and the residue was purified by vacuum distillation to give **5d** as a colorless liquid (4.31 g, 86%); bp 67–69°C/0.55 Torr (Lit.[2a] column chromatography); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.12$ (br s, 1H), 2.51 (t, $J = 6.2$ Hz, 2H), 2.29 (t, $J = 6.4$ Hz, 2H), 1.81–1.66 (m, 4H), 1.53–1.39 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.28, 117.17, 94.74, 36.30, 33.13, 27.05, 26.91, 26.67, 26.26, 25.19$; anal. calcd for $C_{10}H_{15}N$ (149.23): C 80.48; H 10.13; N 9.38; found: C 80.57; H 10.26; N 9.22; IR (film): $\nu = 2213\ cm^{-1}$.

Cyclopentylideneacetonitrile (5a)

Yield: (89%); colorless liquid purified by distillation at bp 72–74°C/10 Torr (Lit.[2a,b] bp 83–84°C/12 Torr).

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Cyclohexylideneacetonitrile (5b)

Yield: (91%); colorless liquid purified by distillation at bp 56–58°C/2 Torr (Lit.[2a,b] bp 86–88°C/10 Torr).

Cycloheptylideneacetonitrile (5c)

Yield (92%); colorless liquid purified by distillation at bp 62–64°C/0.8 Torr or flash column chromatography (Lit.[2a,b] bp 94–95°C/6 Torr or column chromatography).

Cyclooctylideneacetaldehyde (6d); Typical Procedure

To a solution of **5d** (2.1 g, 14.07 mmol) in anhyd Et_2O (35 mL) at −60°C was added in one portion DIBALH (28.14 mL, 1.0 M in hexanes, 28.14 mmol). The stirring was continued for 30 min at −60°C and for 5 hr at 0°C. Then ethyl formate (1.14 mL, 14.07 mmol) was added dropwise over 10 min. After stirring for 60 min the reaction mixture was treated with sat. aq NH_4Cl (28.2 mL) over 20 min. The resulting mixture was warmed to r.t. over 60 min followed by 1 M H_2SO_4 (56.5 mL) over 15 min. The organic layer was separated and the aq phase was extracted with Et_2O (5 × 75 mL). The combined organic phases were washed with 5% $NaHCO_3$ (2 × 100 mL) and brine (100 mL) respectively, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatotron chromatography (silica gel, 100 g, hexanes/ether 5/1 v/v) to afford pure **6d** (1.19 g, 56%) as a colorless liquid. Attempts to purify the crude product **6d** by vacuum distillation gave s colorless mixture (536 mg, 25%); bp 66°C/0.5 Torr of an 1 : 1 ratio approximately of **6d** and its isomer cyclooct-1-en-1-ylacetaldehyde **6e**. Further purification on chromatotron (CH_2Cl_2) provided pure **6d**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.96$ (d, $J = 8.2$ Hz, 1H), 5.84 (d, $J = 8.2$ Hz, 1H), 2.68 (t, $J = 6.2$ Hz, 2H), 2.33 (t, $J = 6.2$ Hz, 2H), 1.81–1.69 (m, 4H), 1.53–1.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 190.73, 172.47, 127.43, 38.35, 29.64, 29.53, 27.36, 26.12, 25.21$ (2 × CH_2); anal. calcd for $C_{10}H_{16}O$ (152.2): C 80.90; H 10.59; found: C 80.92; H 10.57.

Cyclooct-1-en-1-ylacetaldehyde (6e)

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.66$ (t, 1H), 5.54 (t, 1H), 3.0 (d, 2H), 2.09 (br d, 4H), 1.42 (br d, 8H).

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Cyclopentylideneacetaldehyde (6a)

Yield: 2.38 g (52%); flash column chromatography (silica gel, hexanes/Et_2O 4 : 1); pale yellow liquid (Lit.[2b,d]).

Cyclohexylideneacetaldehyde (6b)

Yield: 3.61 g (58%); colorless liquid purified by distillation at bp 44°C/1 Torr; (Lit.[2b–d] bp 52–54°C/2 Torr).

Cycloheptylideneacetaldehyde (6c)

Yield: 5.09 g (89%); pale yellow liquid; flash column chromatography (silica gel, hexanes/Et_2O 4 : 1) (Lit.[2b,c] column chromatography).

Ethyl (2*E*)-4-Cycloalkylidenebut-2-enoates (7)

General Procedure A

A suspension of $LiOH \cdot H_2O$ (2.2 mmol) in anhyd THF (4 mL) was treated at r.t. with **3** (2.2 mmol) followed by aldehyde **6** (2 mmol) and stirred over 2.5 or 16 hr. Then the resulting mixture was filtered through a plug of silica gel eluting with ether (25 mL). The filtrate was concentrated in vacuo and the residue was purified by chromatotron chromatography (2 mm silica gel plate, hexanes/Et_2O 100 : 1.5) to afford esters **7** as colorless liquids in 93–99% (*E*)-stereoselectivity.

General Procedure B

To a solution of triethyl phosphonoacetate **3** (30.06 mmol) in anhyd THF (36 mL) under argon at 0°C was added DMPU (7.58 mL) over 10 min and BuLi (21.8 mL, 1.6 M in hexanes, 34.88 mmol) over 20 min and the stirring was continued for 20 min. Then cooled to −78°C and a solution of aldehyde **6** (17.0 mmol) in THF (36 mL) was added dropwise over 1.5 hr, stirred for 1 hr and the reaction mixture was allowed to warm to 0°C over 1.5 hr. The reaction was quenched with sat. aq NH_4Cl solution (70 mL), extracted with EtOAc (4 × 75 mL) and the combined organic layers were washed successively with H_2O (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$) and then concentrated under reduced pressure. The resulting crude product was purified by flash

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column chromatography on silica gel (hexanes/Et_2O 18 : 1) to yield (*E*)-**7** and (*Z*)-**8**. The R_f for (*Z*)-**8** was found to be higher than (*E*)-**7**.

Ethyl (2*E*)-4-Cyclopentylidenebut-2-enoate (7a)

Procedure A

Yield: **7a** (235 mg, 65%), **8a** (5.8 mg, <2%) reaction time 2.5 hr; **7a** (136 mg, 38%), **8a** (2 mg, <1%) reaction time 16 hr.

Procedure B

Yield: **7a** (1.53 g, 50%) and **8a** (15 mg, <1%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$ (dd, $J = 15.2$, 11.6 Hz, 1H), 6.0 (d, $J = 11.6$ Hz, 1H), 5.62 (d, $J = 15.2$ Hz, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 2.41 (t, $J = 7.1$ Hz, 2H), 2.31 (t, $J = 7.1$ Hz, 2H), 1.68–1.57 (m, 4H), 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 167.59$, 158.91, 142.33, 119.01, 117.59, 59.93, 34.66, 30.03, 26.09, 25.84, 14.23; IR $\nu =$ (film): 1718 cm^{-1}; LC/MS: m/z (%) = 181 [$(M + H)^+$, 100], 173 (3), 163 (8), 153 (15); HRMS (EI): m/z calcd for $C_{11}H_{16}O_2$ 180.11504; found 180.11503.

Ethyl (2*E*)-4-Cyclohexylidenebut-2-enoate (7b)

Procedure A

Yield: **7b** (255 mg, 66%), **8b** (19%, 5%), reaction time 2.5 hr; **7b** (247 mg, 64%), **8b** (18%, 5%), reaction time 16 hr.

Procedure B

Yield: **7b** (2.34 g, 71%) and **8b** (66 mg, 2%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.55$ (dd, $J = 15.0$, 12.0 Hz, 1H), 5.89 (d, $J = 11.9$ Hz, 1H), 5.74 (d, $J = 15.0$ Hz, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 2.41–2.29 (m, 2H), 2.21–2.11 (m, 2H), 1.58–1.54 (m, 6H), 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 167.64$, 154.15, 140.23, 120.45, 118.74, 59.98, 37.66, 29.74, 28.45, 27.84, 26.45, 14.27; IR (film): $\nu = 1713$ cm^{-1}; LC/MS: m/z (%) = 195 [$(M + H)^+$, 88], 149 (100), 131 (4), 121 (7); HRMS (EI): m/z calcd for $C_{12}H_{18}O_2$ 194.13068; found 194.13086.

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Ethyl (2*E*)-4-Cycloheptylidenebut-2-enoate (7c)

Procedure A

Yield: **7b** (169 mg, 41%), **12b** (13 mg, 3%), reaction time 2.5 hr; **7b** (165 mg, 40%), **8b** (4 mg, 1%), reaction time 16 hr.

Procedure B

Yield: **7c** (2.27 g, 64%) and **8c** (31 mg, $<1\%$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.56$ (dd, $J = 14.8$, 11.8 Hz, 1H), 5.96 (d, $J = 11.7$ Hz, 1H), 5.79 (d, $J = 15.1$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.51 (t, $J = 5.4$ Hz, 2H), 2.33 (t, $J = 5.5$ Hz, 2H), 1.69–1.61 (m, 3H), 1.50–1.41 (m, 5H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 167.72$), 156.00, 140.73, 123.55, 118.65, 60.04, 38.50, 30.73, 29.57, 28.88, 27.22, 27.08, 14.33; IR (film): $\nu = 1713\,cm^{-1}$; anal. calcd for $C_{13}H_{20}O_2$ (208.3): C 74.96; H 9.67; found: C 75.40; H 9.72.

Ethyl (2*E*)-4-Cyclooctylidenebut-2-enoate (7d)

Procedure A

Yield: **7d** (258 mg, 58%) and **8d** (12 mg, $<3\%$), reaction time 2.5 hr; **7d** (214 mg, 48%) and **8d** (8 mg, $<2\%$), reaction time 16 hr.

Procedure B

Yield **7d** (2.64 g, 70%) and **8b** (54 mg, 2%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.56$ (dd, $J = 15.1$, 11.8 Hz, 1H), 5.96 (d, $J = 11.8$ Hz, 1H), 5.69 (d, $J = 15.1$ Hz, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 2.41 (t, $J = 6.2$ Hz, 2H), 2.25 (t, $J = 6.2$ Hz, 2H), 1.69–1.64 (m, 4H), 1.48–1.39 (m, 6H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 167.67$, 157.14, 140.68, 123.57, 118.25, 59.94, 38.08, 29.76, 28.37, 27.37, 26.21, 25.78, 25.46, 14.28; IR (film): $\nu = 1713\,cm^{-1}$; LC/MS: m/z (%) = 223 [$(M + H)^+$, 100], 177 (30), 159 (4), 149 (43), 135 (8); HRMS (EI): m/z calcd for $C_{14}H_{22}O_2$ 222.16190; found 222.16198.

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General Procedure for the Preparation of Ethyl (2*Z*)-4-Cycloalkylidenebut-2-enoates (8a–d)

To a solution of **4a/4b** (1 mmol) in THF (3 mL) at −78°C under argon was added dropwise triton B (benzyltriethylammonium hydroxide 40% in MeOH) (0.54 mL, 1.35 mmol) over 15 min. After 30 min, a solution of aldehyde 6 (1.1 mmol) in THF (1 mL) was added dropwise for 20 min and the resulting mixture was gradually warmed to 0°C (see Table 2). The reaction was quenched with sat. aq NH_4Cl (10 mL) extracted with EtOAc (4 × 5 mL) and the combined organic layers were washed successively with H_2O (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$) and then concentrated in vacuo. The crude residue was purified on chromatotron (silica gel, hexanes followed by hexanes/Et_2O 100 : 1.5) to yield a mixture of (*Z*/*E*) products **8/7** determined by ^1H HMR analysis. Further separation of the mixture afforded analytical samples of **8** and **7**, respectively, as colorless liquids.

Ethyl (2*Z*)-4-Cyclopentylidenebut-2-enoate (8a)

From **4a**: Yield: **8a** (85 mg, 47%) and **7a** (30 mg, 17%); from **4b**: Yield: **8a** (101 mg, 56%) and **7a** (27 mg, 15%); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.21$ (d, $J = 12.0$ Hz, 1H), 6.65 (t, $J = 11.6$ Hz, 1H), 5.44 (d, $J = 11.5$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 2.36 (t, $J = 6.4$ Hz, 4H), 1.67–1.56 (m, 4H), 1.2 (t, $J = 7.2$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 166.76$, 159.39, 141.97, 117.67, 113.69, 59.61, 34.80, 29.29, 25.97, 25.75, 14.22; IR (film): $\nu = 1713\ cm^{-1}$; LC/MS: m/z (%) = 181 [$(M + H)^+$, 100], 173 (3), 163 (1); HRMS (EI): m/z calcd for $C_{11}H_{16}O_2$ 180.11503; found 180.11504.

Ethyl (2*Z*)-4-Cyclohexylidenebut-2-enoate (8b)

From **4a**: Yield: **8b** (118 mg, 61%) and **7b** (39 mg, 20%); from **4b**: Yield: **8b** (130 mg, 67%) and **7b** (29 mg, 15%); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.08$ (d, $J = 11.9$ Hz, 1H), 6.84 (t, $J = 11.7$ Hz, 1H), 5.47 (d, $J = 11.4$ Hz, 1H), 4.09 (q, $J = 7.1$ Hz, 2H), 2.27 (br t, 2H), 2.18 (br t, $J = 5.8$ Hz, 2H), 1.51–1.49 (m, 6H), 1.19 (t, $J = 7.1$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 166.84$, 154.48, 139.69, 118.65, 114.89, 59.71, 37.97, 28.94, 28.43, 27.85, 26.54, 14.22; IR (film): $\nu = 1713\ cm^{-1}$; LC/MS: m/z (%) = 195 [$(M + H)^+$, 100), 193 (4), 163 (2), 131 (2), 121 (3); HRMS (EI): m/z calcd for $C_{12}H_{18}O_2$ 194.13096; found 194.13068.

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Ethyl (2*Z*)-4-Cycloheptylidenebut-2-enoate (8c)

From **4a**: Yield: **8c** (93 mg, 45%) and **7c** (27 mg, 13%); from **4b**: Yield: **8c** (159 mg, 76%) and **7c** (20 mg, 10%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.16$ (d, $J = 11.9$ Hz, 1H), 6.87 (t, $J = 11.7$ Hz, 1H), 5.53 (d, $J = 11.4$ Hz, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 2.47 (t, $J = 5.4$ Hz, 2H), 2.39 (t, $J = 5.7$ Hz, 2H), 1.62–1.55 (m, 4H), 1.51–1.46 (m, 4H), 1.27 (t, $J = 7.2$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 166.87$, 157.62, 140.19, 121.71, 114.61, 59.57, 38.69, 30.0, 29.58, 28.71, 28.21, 27.1, 14.24; IR (film): $\nu = 1713\,cm^{-1}$; anal. calcd for $C_{13}H_{20}O_2$ (208.3): C 74.96; H 9.68; found: C 75.00; H 9.64.

Ethyl (2*Z*)-4-Cyclooctylidenebut-2-enoate (8d)

From **4a**: Yield: **8d** (85 mg, 38%) and **7d** (22 mg, 10%); from **4b**: Yield: **8d** (182 mg, 82%) and **7d** (33 mg, 14%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.21$ (d, $J = 12.1$ Hz, 1H), 6.87 (t, $J = 11.7$ Hz, 1H), 5.51 (d, $J = 11.4$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 2.38 (t, $J = 6.1$ Hz, 2H), 2.32 (t, $J = 6.2$ Hz, 2H), 1.70–1.66 (m, 4H), 1.49–1.44 (m, 6H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 166.87$, 157.62, 140.35, 121.85, 114.11, 59.59, 38.52, 29.09, 28.72, 27.53, 26.16, 25.51 ($2 \times CH_2$), 14.28; IR (film): $\nu = 1713\,cm^{-1}$; LC/MS: m/z (%) = 223 [$(M + H)^+$, 80], 177 (69), 149 (8), 149 (100), 159 (4), 135 (14); HRMS (EI): m/z calcd for $C_{14}H_{22}O_2$ 222.16204; found 222.16198.

General Procedure for Preparation of (2*E*)-4-Cycloalkylidenebut-2-enoic Acids (9a–d) and (2Z)-4-Cycloalkylidenebut-2-enoic Acids (10a–d)

A mixture of esters (*E*)-**7** or (*Z*)-**8** (0.44 mmol) and NaOH (1.2 g, 30 mmol) in H_2O/MeOH (7.8/3.9 mL) was gently refluxed for 45 min. After cooling the reaction mixture was diluted with brine (5 mL) and extracted with Et_2O (2×10 mL). The aqueous layer was acidified with 10% HCl until pH 1 was attained, extracted with EtOAc (5×6 mL), and the combined extracts washed with brine (5 mL), dried ($MgSO_4$) and concentrated in vacuo. Chromatotron chromatography (silica gel, hexanes/EtOAc 90 : 10) afforded pure acids (*E*)-**9** or (*Z*)-**10** respectively as a white solid.

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(2*E*)-4-Cyclopentylidenebut-2-enoic Acid (9a)

Yield: 40 mg (60%); mp 112–114°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.43$ (dd, $J = 15.2$, 11.6 Hz, 1H), 6.12 (d, $J = 11.6$ Hz, 1H), 5.67 (d, $J = 15.4$ Hz, 1H), 2.48 (t, $J = 6.9$ Hz, 2H), 2.39 (t, $J = 7.0$ Hz, 2H), 1.79–1.63 (m, 4H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 171.21$, 160.34, 144.21, 120.15, 118.79, 35.61, 30.89, 27.18, 26.94; LC/MS: m/z (%) = 151 [$(M - H)^-$, 100], 106 (18), 62 (5); HRMS (EI): m/z calcd for $C_9H_{12}O_2$ 152.07590; found 152.07570; IR (KBr): $\nu = 1679\,cm^{-1}$.

(2*E*)-4-Cyclohexylidenebut-2-enoic Acid (9b)

Yield: 58 mg (80%); mp 132–134°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (dd, $J = 15.0$ Hz, 1H), 5.99 (d, $J = 11.8$ Hz, 1H), 5.75 (d, $J = 15.1$ Hz, 1H), 2.39 (br s, 2H), 2.26 (br s, 2H), 1.61 (br d, 6H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 171.11$, 155.61, 142.05, 121.57, 119.97, 38.66, 30.65, 29.73, 29.11, 27.59; LC/MS: m/z (%) = 165 [$(M - H)^+$, 100), 131 (7), 113 (25), 69 (15); HRMS (EI): m/z calcd for $C_{10}H_{14}O_2$ 166.09938; found 166.09920; IR (KBr): $\nu = 1680\,cm^{-1}$.

(2*E*)-4-Cycloheptylidenebut-2-enoic Acid (9c)

Yield: 67 mg (85%); mp 88–89°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.58$ (dd, $J = 15.1$, 11.7 Hz, 1H), 6.02 (d, $J = 11.7$ Hz, 1H), 5.74 (d, $J = 15.1$ Hz, 1H), 2.53 (t, $J = 5.8$ Hz, 2H), 2.32 (t, $J = 5.8$ Hz, 2H), 1.75 (br d, 4H), 1.51 (br d, 4H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 171.08$, 157.31, 142.98, 124.69, 119.83, 39.43, 31.58, 30.72, 29.87, 29.37, 28.40; LC/MS: m/z (%) = 179 [$(M - H)^-$, 100], 135 (11), 131 (5), 113 (25), 62 (8); HRMS (EI): m/z calcd for $C_{11}H_{16}O_2$ 180.11503; found 180.11524; IR (KBr): $\nu = 1680\,cm^{-1}$.

(2*E*)-4-Cyclooctylidenebut-2-enoic Acid (9d)

Yield: 76 mg (89%); mp 114–116°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$ (dd, $J = 15.1$, 11.8 Hz, 1H), 6.07 (d, $J = 11.8$ Hz, 1H), 5.72 (d, $J = 15.1$ Hz, 1H), 2.47 (t, $J = 6.2$ Hz, 2H), 2.32 (t, $J = 6.1$ Hz, 2H), 1.75 (br d, 4H), 1.51 (br d, 6H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 171.21$, 158.63, 142.57, 124.76, 119.39, 39.22, 30.66, 29.75, 28.59, 27.26, 26.69, 26.65; LC/MS: m/z

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(%) = 193 [(M − H)$^-$, 100], 167 (3), 155 (2), 131 (4); HRMS (EI): m/z calcd for $C_{12}H_{18}O_2$ 194.13068; found 194.13064; IR (KBr): $\nu = 1680\,cm^{-1}$.

(2Z)-4-Cyclopentylidenebut-2-enoic Acid (10a)

Yield: 42 mg (63%); mp 105–107°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.19$ (d, $J = 12.0$ Hz, 1H), 6.79 (t, $J = 11.6$ Hz, 1H), 5.49 (d, $J = 11.4$ Hz, 1H), 2.47–2.39 (m, 4H), 1.79–1.62 (m, 4H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 170.52$, 160.10, 143.33, 119.03, 115.22, 35.74, 30.16, 27.09, 26.87; LC/MS: m/z (%) = 151 [(M − H)$^-$, 100], 141 (4), 113 (48), 59 (6); HRMS (EI): m/z calcd for $C_9H_{12}O_2$ 152.08373; found 152.08352; IR (KBr): $\nu = 1684\,cm^{-1}$.

(2Z)-4-Cyclohexylidenebut-2-enoic Acid (10b)

Yield: 50 mg (68%); mp 121–123°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.06$ (d, $J = 12.1$ Hz, 1H), 7.0 (d, $J = 11.1$ Hz, 1H), 5.53 (d, $J = 11.0$ Hz, 1H), 2.39 (br t, 2H), 2.34 (br t, 2H), 1.61 (br s, 6H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 170.34$, 155.27, 141.14, 119.96, 116.27, 39.07, 29.84 (2 × CH_2), 29.14, 27.71; LC/MS: m/z (%) = 165 [(M − H)$^-$, 41], 131 (4), 113 (100), 69 (50); HRMS (EI): m/z calcd for $C_{10}H_{14}O_2$ 166.09938; found 166.09922; IR (KBr): $\nu = 1680\,cm^{-1}$.

(2Z)-4-Cycloheptylidenebut-2-enoic Acid (10c)

Yield: 68 mg (86%); mp 86–88°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.12$ (d, $J = 11.9$ Hz, 1H), 6.94 (t, $J = 11.8$ Hz, 1H), 5.53 (d, $J = 11.4$ Hz, 1H), 2.51 (t, $J = 5.3$ Hz, 2H), 2.39 (t, $J = 5.5$ Hz, 2H), 1.65–1.64 (m, 4H), 1.54–1.52 (m, 4H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 170.28$, 156.97, 141.62, 123.12, 115.99, 39.76, 30.89, 30.76, 29.84, 29.51, 28.34; anal. calcd for $C_{11}H_{16}O_2$ (180.2): C 73.29; H 8.94; found: C 73.14; H 9.00; IR (KBr): $\nu = 1684\,cm^{-1}$.

(2Z)-4-Cyclooctylidenebut-2-enoic Acid (10d)

Yield: 55 mg (64%); mp 110–112°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.16$ (d, $J = 12.1$ Hz, 1H), 6.97 (t, $J = 11.7$ Hz, 1H), 5.53 (d, $J = 11.4$ Hz, 1H), 2.45 (t, $J = 6.1$ Hz, 2H), 2.33 (t, $J = 6.2$ Hz, 2H), 1.79–1.68 (m, 4H,

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1.58–1.46 (m, 6H); ^{13}C (75 MHz, $CDCl_3$): $\delta = 170.34$, 158.25, 141.68, 123.28, 115.60, 39.63, 29.98, 29.80, 28.66, 27.27, 26.74, 26.70; LC/MS: m/z (%) = 193 [$(M - H)^-$, 100], 167 (4), 155 (5), 131 (4), 113 (21); HRMS (EI): m/z calcd for $C_{12}H_{18}O_2$ 194.13068; found 194.13098; IR (KBr): $\nu = 1684\,cm^{-1}$.

General Procedure for the Preparation of Sodium (2*E*)-4-Cycloalkylidenebut-2-enoates (11a–d) and Sodium (2*Z*)-4-Cycloalkylidenebut-2-enoates (12c,d)

To a solution of acid (*E*)-**9** or (*Z*)-**10** (2.4 mmol) in dry MeOH (10 mL) was added dropwise a solution of NaOH (2.18 mmol) in MeOH (20 mL) at 0°C under argon and the resulting mixture was warmed to r.t. overnight. The MeOH was concentrated under reduced pressure and the white solid formed was filtered, washed successfully with Et_2O (5 × 25 mL), and dried in vacuo to give pure sodium salt ((E)-**11**)/((Z)-**12**) as a white solid; mp > 300°C.

Sodium (2*E*)-4-Cyclopentylidenebut-2-enoate (11a)

White solid; yield: 330 mg (87%); mp > 300°C; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.35$ (dd, $J = 15.2$, 11.3 Hz, 1H), 6.03 (d, $J = 11.3$ Hz, 1H), 5.73 (d, $J = 15.1$ Hz, 1H), 2.46 (t, $J = 6.4$ Hz, 2H), 2.36 (t, $J = 6.4$ Hz, 2H), 1.73–1.63 (m, 4H); HR (-LSIMS): calcd for $C_9H_{11}O_2Na$ 151.07590 (M − Na); found 151.07578.

Sodium (2*E*)-4-Cyclohexylidenebut-2-enoate (11b)

White solid; yield: 369 mg (90%); mp > 300°C; ^{1}H NMR (200 MHz, CD_3OD): $\delta = 7.40$ (dd, $J = 15.0$, 11.6 Hz, 1H), 6.0 (d, 1H), 5.8 (d, $J = 15.1$ Hz, 1H), 2.4 (br s, 2H), 2.2 (br s, 2H), 1.6 (br s, 6H); HR (-LSIMS): calcd for $C_{10}H_{13}O_2Na$ 165.09155 (M − Na); found 165.09124.

Sodium (2*E*)-4-Cycloheptylidenebut-2-enoate (11c)

White solid; yield: 339 mg (77%); mp > 300°C; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.35$ (dd, $J = 15.1$, 11.5 Hz, 1H), 5.93 (d, $J = 11.5$ Hz, 1H), 5.78 (d, $J = 15.1$ Hz, 1H), 2.51 (t, $J = 5.8$ Hz, 2H), 2.33 (t, $J = 5.8$ Hz, 2H),

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1.73–1.63 (m, 4H), 1.57–1.52 (m, 4H); HR (-LSIMS): calcd for $C_{11}H_{15}O_2Na$ 179.10720 (M − Na); found 179.10689.

Sodium (2*E*)-4-Cyclooctylidenebut-2-enoate (11d)

White solid; yield: 358 mg (76%); mp > 300°C; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.39$ (dd, $J = 15.1$, 11.6 Hz, 1H), 5.97 (d, $J = 11.7$ Hz, 1H), 5.77 (d, $J = 15.1$ Hz, 1H), 2.45 (t, $J = 6.2$ Hz, 2H), 2.28 (t, $J = 6.2$ Hz, 2H), 1.78–1.71 (m, 4H), 1.66–1.51 (m, 6H); HR (-LSIMS): calcd for $C_{12}H_{17}O_2Na$ 193.12285 (M − Na); found 193.12268.

Sodium (2*Z*)-4-Cycloheptylidenebut-2-enoate (12c)

White solid; yield: 414 mg (94%); mp > 300°C; ^{1}H NMR (300 MHz, CD_3OD): $\delta = 6.97$ (d, $J = 11.8$ Hz, 1H), 6.51 (d, $J = 11.6$ Hz, 1H), 5.65 (d, $J = 11.5$ Hz, 1H), 2.44 (t, $J = 5.9$ Hz, 2H), 2.34 (t, $J = 6.4$ Hz, 2H), 1.63 − 1.59 (m, 4H), 1.56–1.51 (m, 4H).

Sodium (2*Z*)-4-Cyclooctylidenebut-2-enoate (12d)

Yield: 433 mg (92%); mp > 300°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.04$ (d, $J = 12.0$ Hz, 1H), 6.56 (d, $J = 11.7$ Hz, 1H), 5.48 (d, $J = 11.5$ Hz, 1H), 2.39 (t, $J = 6.1$ Hz, 2H), 2.29 (t, $J = 6.3$ Hz, 2H), 1.71 (m, 4H), 1.51 (br s, 6H).

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