Stereoselective Vinylogous Mukaiyama Aldol Reaction of α-Haloenals

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We have developed a high-yielding and stereoselective vinylogous Mukaiyama aldol reaction (VMAR) of α-haloenals. Contrary to the simple α,β-unsaturated aldehyde, α-haloenals were found to be reactive affording the corresponding VMAR adducts in excellent yields. Some transformations of VMAR adducts by Pd-mediated cross-coupling were also examined in order to demonstrate the synthetic utility of VMAR of α-haloenals.

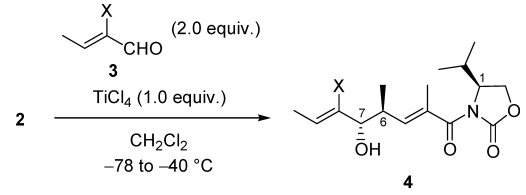
Key words vinylogous Mukaiyama aldol reaction; α-haloenal; stereoselectivity; cross-coupling

We previously reported a highly stereoselective vinylogous Mukaiyama aldol reaction (VMAR) using vinylketene silyl *N*,*O*-acetal **1** and **2**, which provides a unique and remarkable entry to a remote asymmetric induction (Chart 1).[1—3] From a synthetic point of view, this method can directly afford the *anti*-δ-hydroxy-α,γ-dimethyl-α,β-unsaturated carbonyl unit which is seen in many naturally occurring products. Indeed, VMAR has successfully been utilized in natural product syntheses by many groups[4—20] including ourselves.[21—25] However, α,β-unsaturated aldehyde is not generally a good substrate for VMAR in terms of yield (*i.e.*, low to moderate). High yield could be achieved by the addition of a catalytic amount of water,[3] or by carrying out the reaction for a prolonged period of time.[5,11] In this context, we became interested in the employment of α-haloenals as substrates which are considered to be much more reactive compared to simple enals. We also reasoned that the VMAR products from α-haloenals could serve as versatile intermediates for introducing a variety of substituents using well-established Pd-mediated methodologies. Herein, we report a high-yielding and stereoselective VMAR of α-haloenals achieved under standard conditions ($TiCl_4$ in CH_2Cl_2, 2.0 eq of aldehyde). Some transformations of VMAR products from α-haloenals by Pd-catalyzed cross-coupling are also described.

In this study, we examined VMAR of α-iodoenal **3a**,[26] α-bromoenal **3b**,[27] and α-chloroenal **3c**[28,29] (Table 1). According to the established protocol, VMAR of α-iodoenal **3a** (2.0 eq) with the vinylketene silyl *N*,*O*-acetal **2** using $TiCl_4$ (1.0 eq) afforded the corresponding *anti*-aldol adduct **4a** in excellent yield with high diastereoselectivity (entry 1). In addition, VMAR of α-bromoenal **3b** and α-chloroenal **3c** also provided *anti*-adducts **4b** and **4c**[30] in excellent yield, respectively (entries 2, 3). Notably, α-halo substituents improved the yields of aldol adducts and shortened the reaction time compared with VMAR of tiglic aldehyde **3d** (entry 4). Independently, Hosokawa and Tatsuta *et al.* reported that the VMAR of *ent*-**2** and tiglic aldehyde **3d** afforded *ent*-**4d** in good yield (82%) over a prolonged reaction time (4 d) at low temperature (−60 °C).[5,11]

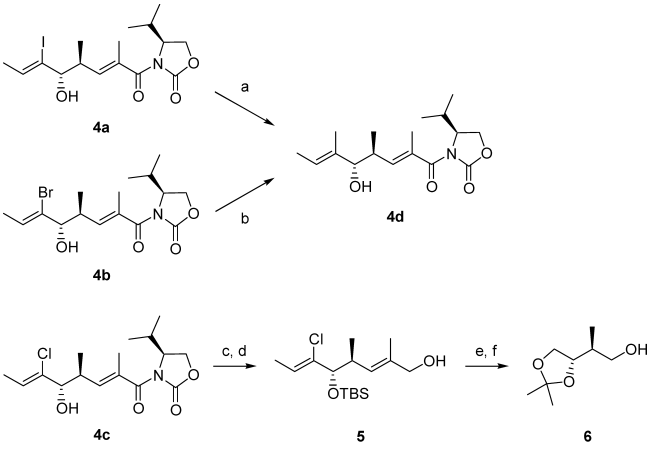
Stereochemical determination of the aldol adducts **4a** and **4b** were easily achieved by Stille cross-coupling using a catalytic amount of $Pd(dba)_2$ and Me_4Sn to convert the *anti*-adduct **4d** (Chart 2). The spectroscopic data of synthetic **4d**

Table 1. VMAR of α-Haloenals



Entry	X		Time (h)	Yield (%)	d.r.[a]
1	I	**3a**	10	95	>20 : 1
2	Br	**3b**	12	88	>20 : 1
3	Cl	**3c**	4	93	>20 : 1
4	Me	**3d**	14	76	>20 : 1

a) Diastereomeric ratio was determined by ^{1}H-NMR analysis.



Reagents and conditions: (a) Me_4Sn, $Pd(dba)_2$, Ph_3As, HMPA, 60 °C, 92%; (b) Me_4Sn, $Pd(dba)_2$, HMPA, 60 °C, 11% (brsm 72%); (c) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 100%; (d) $NaBH_4$, THF–H_2O, RT, 99%; (e) O_3, CH_2Cl_2–MeOH, −78 °C then $NaBH_4$, RT, 38%; (f) *p*-TsOH, acetone, RT, quant.

Chart 2. Determination of the Stereochemistry of **4a**, **4b** and **4c**

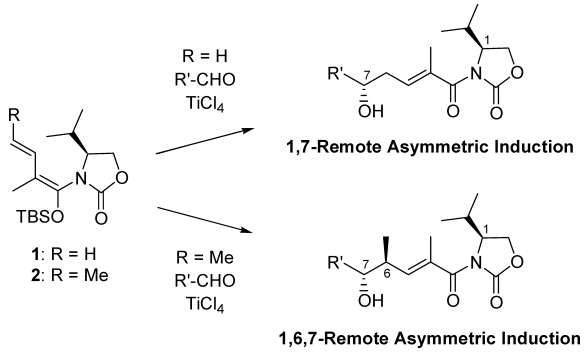


Chart 1. Vinylogous Mukaiyama Aldol Reaction

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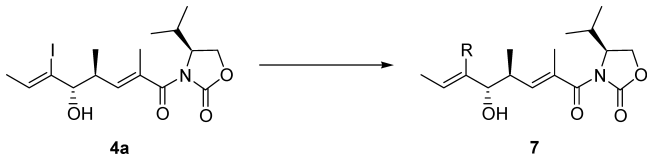
Table 2. Pd-Mediated Cross-Coupling with Vinyl Iodide **4a**



Entry	Conditions	R		Yield (%)
1	Me_4Sn, $Pd(dba)_2$, $AsPh_3$, HMPA, 60 °C	Me	**4d**	92
2	Et_2Zn, $Pd(PPh_3)_4$, THF, 0 °C to RT	Et	**7a**	72
3	$CH_2{=}CHSnBu_3$, $Pd(dba)_2$, $AsPh_3$, HMPA, RT		**7b**	96

from **4a** and **4b** agreed with those of the known *ent*-**4d**.[11] (Synthetic **4d**: $[\alpha]_D^{25}$ −17.3, c=1.09 in CH_2Cl_2, reported *ent*-**4d**: $[\alpha]_D^{25}$ +16.5, c=1.16 in CH_2Cl_2).

Stereochemistry of the aldol adduct **4c** was determined by transforming to the known compound **6**.[31] After protection of the secondary alcohol with TBSOTf, the chiral auxiliary group was reductively removed with $NaBH_4$ to provide the alcohol **5**. Ozonolysis of **5**, reduction of the resulting aldehyde, followed by acetal formation gave the known compound **6**. The spectroscopic data of synthetic **6** was identical to those reported for **6**.[31]

Next, a series of representative Pd-catalyzed cross-coupling reactions were applied to vinyl iodide **4a** in order to demonstrate the synthetic utility of the present approach (Table 2). Introduction of methyl group to **4a** (entry 1) is already described in Chart 2. Negishi cross-coupling with Et_2Zn and $Pd(PPh_3)_4$ afforded ethyl derivative **7a** in 72% yield (entry 2). Introduction of a vinyl group to **4a** was performed by Stille cross-coupling to afford **7b** in excellent yield (entry 3).

In conclusion, we were able to overcome the low reactivity of enals in VMAR by employing α-haloenals as substrates. Moreover, the combination of VMAR of α-haloenal and well-established Pd-catalyzed cross-coupling has been demonstrated to considerably expand the scope of VMAR.

Experimental

General Techniques All non-aqueous reactions were carried out under an argon atmosphere in oven-dried of flame-dried glassware. Tetrahydrofuran (THF) and Et_2O were purchased from Kanto Chemical Co., Inc., Tokyo, Japan in anhydrous grade. CH_2Cl_2 was distilled from CaH_2 immediately before use. $TiCl_4$ was distilled from granular cupper and stored in ampoules. Diisopropylethylamine was distilled from CaH_2 and stored over KOH. Other reagents were used as received. All reactions were monitored by TLC, which was carried out on 0.25 mm Silica Gel 60 F_{254} plates (E. Merck). Flash column chromatography separations were performed on PSQ 100B (Fuji Silysia Co., Ltd., Japan). The NMR spectra (^1H, ^{13}C) were determined on a Bruker 600 MHz spectrometer (Avance DRX-600) or on a JEOL 400 MHz spectrometer (JNM-LD400), using $CDCl_3$ solutions, unless otherwise noted. Chemical shifts for ^1H-NMR were expressed in parts per million (ppm) downfield from tetramethylsilane (δ) in duteriochloroform as internal standard and coupling constants (J) are in hertz (Hz). Multiplicities are indicated as: br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Melting points were determined with SHIMADZU MM-2 or Yanaco MP-3S melting point apparatus and were uncorrected. Optical rotations were recorded using $CHCl_3$ or CH_2Cl_2 as solvents on a JASCO P-1030 digital polarimeter at room temperature, using sodium D line. Infrared spectra (IR) were recorded on a JASCO FT/IR-410 spectrometer using NaCl (neat) or KBr pellets (solid), and are reported in wavenumbers (cm^{-1}). Mass spectra (MS) were obtained on an Applied Biosystems mass spectrometer (API QSTAR pulsar i) under conditions as High resolution, using poly(ethylene glycol) as internal standard.

General Procedure for Vinylogous Mukaiyama Aldol Reaction of Vinylketene Silyl *N*,*O*-Acetal 2 with α-Haloenals To a solution of aldehyde (1.41 mmol, 2.0 eq) in CH_2Cl_2 (3.5 ml), a 1.0 M $TiCl_4$ solution in CH_2Cl_2 (0.70 ml, 0.705 mmol, 1.0 eq) was added dropwise at −78 °C. Then a solution of **1** (239 mg, 0.705 mmol) in CH_2Cl_2 (3.5 ml) was added dropwise into the aldehyde solution at −78 °C. After stirring for 4 to 16 h at −40 °C, the cold reaction mixture was poured into 1 : 1 mixture of saturated $NaHCO_3$ aq. and saturated Rochelle salt aq. (25 ml). The mixture was diluted with Et_2O (25 ml), and stirred vigorously at room temperature until the white slurry was completely dissolved. The aqueous layer was extracted two times with Et_2O. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt) to give the aldol adducts.

Aldol adduct **4a**: TLC, *Rf*=0.28 (hexane/AcOEt=2 : 1). mp 114 °C. ^1H-NMR (600 MHz, $CDCl_3$) δ: 0.86 (3H, d, J=6.6 Hz), 0.93 (3H, d, J=6.9 Hz), 0.94 (3H, d, J=7.0 Hz), 1.84 (3H, d, J=6.4 Hz), 2.02 (3H, d, J=1.3 Hz), 2.36 (1H, dqq, J=4.7, 7.0, 6.9 Hz), 2.94 (1H, ddq, J=10.5, 9.0, 6.6 Hz), 3.30 (1H, dd, J=9.0, 2.4 Hz), 3.64 (1H, d, J=2.4 Hz), 4.20 (1H, dd, J=9.1, 5.6 Hz), 4.35 (1H, dd, J=9.1, 9.1 Hz), 4.58 (1H, ddd, J=9.1, 5.6, 4.7 Hz), 5.82 (1H, dq, J=10.5, 1.3 Hz), 6.02 (1H, q, J=6.4, Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 14.3, 15.2, 16.0, 17.8, 21.4, 28.5, 40.0, 58.1, 63.5, 81.7, 113.9, 133.0, 133.5, 139.3, 154.4, 171.3. $[\alpha]_D^{24}$ −26.6 (c=1.00, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) 3486, 2965, 1769, 1687, 1366, 1301, 1209. high resolution (HR)-MS (electrospray ionization (ESI)) *m*/*z*: 444.0644 (Calcd for $C_{16}H_{24}NO_4NaI$ $[M+Na]^+$ 444.0642).

Aldol adduct **4b**: TLC, *Rf*=0.52 (hexane/AcOEt=2 : 1). ^1H-NMR (600 MHz, $CDCl_3$) δ: 0.90 (3H, d, J=6.6 Hz), 0.93 (3H, d, J=6.9 Hz), 0.94 (3H, d, J=7.0 Hz), 1.81 (3H, d, J=6.5 Hz), 2.01 (3H, d, J=1.4 Hz), 2.36 (1H, dqq, J=4.6, 7.0, 6.9 Hz), 3.02 (1H, ddq, J=10.4, 8.7, 6.6 Hz), 3.59 (1H, d, J=2.8 Hz), 3.79 (1H, dd, J=8.7, 2.8 Hz), 4.20 (1H, dd, J=9.0, 5.5 Hz), 4.35 (1H, dd, J=9.0, 9.0 Hz), 4.58 (1H, ddd, J=9.0, 5.5, 4.6 Hz), 5.77 (1H, dq, J=10.4, 1.4 Hz), 6.07 (1H, q, J=6.5 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 14.2, 15.2, 16.1, 16.4, 17.8, 28.5, 38.5, 58.1, 63.5, 80.7, 127.6, 129.6, 132.9, 139.7, 154.4, 171.3. $[\alpha]_D^{24}$ −16.7 (c=1.15, $CHCl_3$). IR (neat, cm^{-1}) 3494, 2965, 2875, 1772, 1685, 1455, 1367, 1301, 1209. HR-MS (ESI) *m*/*z*: 396.0769 (Calcd for $C_{16}H_{24}NO_4NaBr$ $[M+Na]^+$ 396.0780).

Aldol adduct **4c**: TLC, *Rf*=0.29 (hexane/AcOEt=2 : 1). ^1H-NMR (600 MHz, $CDCl_3$) δ: 0.92 (3H, d, J=6.6 Hz), 0.93 (3H, d, J=7.0 Hz), 0.94 (3H, d, J=7.1 Hz), 1.80 (3H, d, J=6.6 Hz), 2.00 (3H, d, J=1.4 Hz), 2.35 (1H, dqq, J=4.6, 7.1, 7.0 Hz), 3.02 (1H, ddq, J=10.4, 8.8, 6.6 Hz), 3.54 (1H, d, J=3.0 Hz), 3.90 (1H, dd, J=8.8, 3.0 Hz), 4.20 (1H, dd, J=9.0, 5.5 Hz), 4.35 (1H, dd, J=9.0, 9.0 Hz), 4.58 (1H, ddd, J=9.0, 5.5, 4.6 Hz), 5.75 (1H, dq, J=10.4, 1.4 Hz), 5.85 (1H, q, J=6.6 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 13.7, 14.1, 15.2, 16.1, 17.8, 28.5, 37.7, 58.1, 63.5, 80.0, 124.5, 132.8, 134.8, 139.9, 154.4, 171.3. $[\alpha]_D^{24}$ −14.7 (c=1.00, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) 3494, 2965, 2875, 1770, 1687, 1390, 1367, 1315, 1209. HR-MS (ESI) *m*/*z*: 352.1281 (Calcd for $C_{16}H_{24}NO_4NaCl$ $[M+Na]^+$ 352.1286).

Aldol adduct **4d**: TLC, *Rf*=0.34 (hexane/AcOEt=2 : 1). ^1H-NMR (600 MHz, $CDCl_3$) δ: 0.82 (3H, d, J=6.7 Hz), 0.93 (3H, d, J=6.8 Hz), 0.94 (3H, d, J=7.0 Hz), 1.64 (3H, dd, J=6.6, 1.0 Hz), 1.67 (3H, dd, J=1.0 Hz), 1.98 (3H, d, J=1.5 Hz), 2.35 (1H, dqq, J=4.6, 7.0, 6.8 Hz), 2.75 (1H, ddq, J=10.3, 9.3, 6.7 Hz), 3.33 (1H, br s), 3.67 (1H, br d, J=9.3 Hz), 4.19 (1H, dd, J=9.0, 5.7 Hz), 4.35 (1H, dd, J=9.0, 9.0 Hz), 4.58 (1H, ddd, J=9.0, 5.7, 4.6 Hz), 5.48 (1H, dq, J=6.6, 1.0 Hz), 5.78 (1H, dq, J=10.3, 1.5 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 10.5, 13.1, 14.0, 15.2, 16.1, 17.8, 28.4, 37.8, 58.1, 63.4, 82.2, 123.7, 131.7, 134.8, 142.0, 154.5, 171.5. $[\alpha]_D^{24}$ −17.3 (c=1.09, CH_2Cl_2). IR (neat, cm^{-1}) 3513, 2965, 2929, 2873, 1768, 1687, 1367, 1301, 1280, 1211. HR-MS (ESI) *m*/*z*: 332.1822 (Calcd for $C_{17}H_{27}NO_4Na$ $[M+Na]^+$ 332.1832).

Alcohol **5**: To a solution of **4c** (38.5 mg, 0.117 mmol) in CH_2Cl_2 (1.2 ml), *i*-Pr_2NEt (0.061 ml, 0.350 mmol) and TBSOTf (0.064 ml, 0.280 mmol) was added at 0 °C. After stirring for 40 min, the reaction was quenched with MeOH. After stirring further 10 min, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt=8 : 1) to give the corresponding TBS ether (51.8 mg, 100% yield). To a solution of the corresponding TBS ether (49.7 mg, 0.112 mmol) in THF (2.8 ml), $NaBH_4$ (29.6 mg, 0.783 mmol) in water (0.6 ml) was added at 0 °C. After stirring for 3 h at r.t., the reaction was diluted with water and Et_2O. The aqueous layer was extracted two times with Et_2O. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt=8 : 1) to give alcohol **5** (35.2 mg, 99% yield). Alcohol **5**: colorless oil. TLC,

Rf=0.59 (hexane/AcOEt=2 : 1). ^{1}H-NMR (600 MHz, $CDCl_3$) δ: −0.01 (3H, s), 0.01 (3H, s), 0.86 (9H, s), 0.88 (3H, d, *J*=6.9 Hz), 1.16 (1H, t, *J*=6.2 Hz), 1.67 (3H, d, *J*=1.3 Hz), 1.73 (3H, d, *J*=6.6 Hz), 2.80 (1H, ddq, *J*=9.7, 6.5, 6.9 Hz), 3.88 (1H, d, *J*=6.5 Hz), 3.99 (2H, d, *J*=6.2 Hz), 5.23 (1H, dq, *J*=9.7, 1.3 Hz), 5.71 (1H, q, *J*=6.6 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: −5.1, −4.8, 13.4, 14.1, 17.4, 18.1, 25.7, 36.4, 69.1, 80.5, 121.5, 128.3, 135.4, 136.8. $[\alpha]_D^{21}$ −15.2 (*c*=1.02, $CHCl_3$); IR (neat, cm^{-1}) 3328, 2958, 2929, 2857, 1660, 1461, 1255, 1095, 1006. HR-MS (ESI) *m/z*: 341.1658 (Calcd for $C_{16}H_{31}O_2NaSiCl$ $[M+Na]^+$ 341.1674).

Alcohol **6**: Alcohol **5** (12.1 mg, 0.0379 mmol) was diluted in 1 : 1 CH_2Cl_2/MeOH (2.0 ml) and cooled to −78 °C. Ozone was bubbled through the solution until a blue tint was observed (about 3 min), and then argon was passed through the solution for 15 min, after which $NaBH_4$ (11.5 mg, 0.303 mmol) was added. After stirring for 8 h at r.t., the reaction was quenched with saturated NH_4Cl aq. The aqueous layer was extracted two times with Et_2O. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt=2 : 1) to give the corresponding diol (3.4 mg, 38% yield). To a solution of the corresponding diol (2.2 mg, 9.39 mmol) in acetone (0.5 ml), *p*-TsOH (0.9 mg, 4.69 mmol) was added at r.t. After stirring for 16 h, the reaction was neutralized with saturated $NaHCO_3$ aq. The aqueous layer was extracted two times with Et_2O. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with petroleum ether/ether=4 : 1) to give alcohol **6** (1.5 mg, quantitative yield). Alcohol **6**: colorless oil. TLC, *Rf*=0.39 (hexane/AcOEt=1 : 1). ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.83 (3H, d, *J*=7.0 Hz), 1.37 (3H, s), 1.42 (3H, s), 1.89—1.82 (1H, m), 2.75 (1H, dd, *J*=8.6, 2.8 Hz), 3.66 (1H, dd, *J*=8.1, 7.5 Hz), 3.69—3.59 (2H, m), 3.95 (1H, ddd, *J*=8.8, 7.5, 6.1 Hz), 4.10 (1H, dd, *J*=8.1, 6.1 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 13.1, 25.7, 26.7, 39.2, 67.5, 68.8, 80.9, 109.4. $[\alpha]_D^{22}$ +30 (*c*=0.027, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) 2921, 2852, 2042, 1070, 1045, 804. HR-MS (ESI) *m/z*: 183.0993 (Calcd for $C_8H_{16}O_3Na$ $[M+Na]^+$ 183.0997).

Methyl derivative **4d**: To a solution of iodide **4a** (30.0 mg, 0.071 mmol) in degassed HMPA (0.8 ml), Me_4Sn (0.04 ml, 0.285 mmol), $Pd(dba)_2$ (4.1 mg, 0.007 mmol) and $AsPh_3$ (8.7 mg, 0.028 mmol) were added respectively at r.t. After stirring for 40 min at 60 °C, the reaction mixture was poured into H_2O. The mixture was diluted with Et_2O, and the aqueous layer was extracted two times with Et_2O. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt=6 : 1) to give **4d** (20.2 mg, 92% yield).

Ethyl derivative **7a**: To a solution of iodide **4a** (10.7 mg, 0.025 mmol) in degassed HMPA (0.5 ml), $Pd(dba)_2$ (1.5 mg, 0.0025 mmol) and $AsPh_3$ (3.1 mg, 0.010 mmol) were added respectively at r.t. Then a 1.08 M Et_2Zn solution in hexane (0.094 ml, 0.102 mmol) was added dropwise at 0 °C. After stirring for 2 h at r.t., the reaction mixture was quenched with saturated NH_4Cl aq. The aqueous layer was extracted two times with Et_2O. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt=6 : 1) to give **7a** (5.9 mg, 72% yield). Ethyl derivative **7a**: TLC, *Rf*=0.38 (hexane/AcOEt=2 : 1). ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.86 (3H, d, *J*=6.6 Hz), 0.93 (3H, d, *J*=6.9 Hz), 0.94 (3H, d, *J*=7.0 Hz), 1.08 (3H, t, *J*=7.6 Hz), 1.67 (3H, d, *J*=6.8 Hz), 1.98 (3H, d, *J*=1.4 Hz), 2.22—2.11 (2H, m), 2.35 (1H, dqq., *J*=4.6, 7.0, 6.9 Hz), 2.76 (1H, ddq, *J*=10.3, 9.2, 6.6 Hz), 3.30 (1H, d, *J*=1.9 Hz), 3.70 (1H, br d, *J*=9.2 Hz), 4.19 (1H, dd, *J*=9.0, 5.8 Hz), 4.34 (1H, dd, *J*=9.0, 9.0 Hz), 4.58 (1H, ddd, *J*=9.0, 5.8, 4.6 Hz), 5.47 (1H, q, *J*=6.8, Hz), 5.80 (1H, dq, *J*=10.3, 1.4 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 13.0, 13.98, 14.01, 15.2, 16.5, 17.8, 19.8, 28.5, 38.5, 58.1, 63.5, 81.8, 123.5, 131.7, 141.0, 142.2, 154.4, 171.5. $[\alpha]_D^{24}$ −62 (*c*=0.013, $CHCl_3$). IR (neat, cm^{-1}) 3515, 2964, 2931, 2873, 1772, 1685, 1390, 1365, 1301, 1280, 1209. HR-MS (ESI) *m/z*: 346.1996 (Calcd for $C_{18}H_{29}NO_4Na$ $[M+Na]^+$ 346.1988).

Vinyl derivative **7b**: To a solution of iodide **4a** (30.2 mg, 0.072 mmol) in degassed HMPA (0.8 ml), vinyl(tributyl)tin (45.5 mg, 0.143 mmol), $Pd(dba)_2$ (4.1 mg, 0.007 mmol) and $AsPh_3$ (8.8 mg, 0.029 mmol) were added respectively at r.t. After stirring for 10 min at r.t., the reaction mixture was poured into H_2O. The mixture was diluted with Et_2O, and the aqueous layer was extracted two times with Et_2O. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane, then hexane/AcOEt=8 : 1) to give **7b** (22.2 mg, 96% yield). Vinyl derivative **7b**: TLC, *Rf*=0.48 (hexane/AcOEt=2 : 1). ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.87 (3H, d, *J*=6.7 Hz), 0.93 (3H, d, *J*=6.9 Hz), 0.94 (3H, d, *J*=7.0 Hz), 1.79 (3H, d, *J*=7.0 Hz), 1.96 (3H, d, *J*=1.5 Hz), 2.35 (1H, dqq, *J*=4.6, 7.0, 6.9 Hz), 2.94 (1H, ddq, *J*=10.4, 8.7, 6.7 Hz), 3.37 (1H, d, *J*=2.4 Hz), 3.97 (1H, dd, *J*=8.7, 2.4 Hz), 4.20 (1H, dd, *J*=9.0, 5.7 Hz), 4.35 (1H, dd, *J*=9.0, 9.0 Hz), 4.59 (1H, ddd, *J*=9.0, 5.7, 4.6 Hz), 5.24 (1H, br d, *J*=11.5 Hz), 5.51 (1H, dd, *J*=17.8, 1.7 Hz), 5.73 (1H, q, *J*=7.0 Hz), 5.83 (1H, dq, *J*=10.4, 1.3 Hz), 6.58 (1H, dd, *J*=17.8, 11.5 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 13.5, 14.0, 15.2, 16.5, 17.8, 28.5, 39.1, 58.1, 63.5, 79.0, 115.9, 126.9, 131.2, 131.7, 137.5, 142.1, 154.5, 171.5. $[\alpha]_D^{24}$ −51 (*c*=0.19, $CHCl_3$). IR (neat, cm^{-1}) 3505, 2965, 2929, 2875, 1770, 1685, 1390, 1367, 1301, 1211. HR-MS (ESI) *m/z*: 344.1844 (Calcd for $C_{18}H_{27}NO_4Na$ $[M+Na]^+$ 344.1832).

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