Enantioselective Synthesis of 2,2-Dialkyl-3-butenals by Alkylation of (4*S*,5*S*)-ADPD-imines

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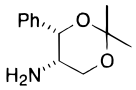
(*S*)-2-Alkyl-2-methyl-3-butenals that have a quaternary stereogenic carbon atom at the α-position were obtained from 2-methyl-2-butenal (4*S*,5*S*)-ADPD-imine in good enantioselective excesses (up to 81% ee). Using this reaction, a novel sesquiterpene, (+)-(*E*)-2,5,9-trimethyl-2-vinyl-4,8-decadienal, was synthesized with moderate enantioselectivity (53% ee).

The enantioselective synthesis of α-substituted carbonyl compounds has been one of the most important goals in organic synthesis. Especially α-substituted-*β*,*γ*-unsaturated aldehyde or ketone subunits are found in a very broad range of bioactive compounds and natural products, e.g., in vitamin E side chain,[1] pseudomonic acid,[2] stigmastatriene,[3] and levuglandin.[4] There are few methods for construction of an asymmetric quaternary carbon atom such as α,α-disubstituted-*β*,*γ*-unsaturated aldehydes in organic synthesis. We have previously reported the enantioselective synthesis of 2-alkyl-2-methyl-3-butenenitriles which have a quaternary carbon at the α-position by diastereoselective alkylation of 2-methyl-2-butenal SAMP ((*S*)-1-amino-2-(methoxymethyl)pyrrolidinyl)-hydrazone.[5] In the application of this method for the synthesis of α,α-disubstituted-*β*,*γ*-unsaturated aldehyde, the cleavage of the SAMP-hydrazone unit was difficult.[6a] On the other hand, in the synthesis of (±)-2,2-dialkylbutenals **4** by alkylation of 2-alkyl-2-butenal cyclohexylimine or bisalkylation of 2-butenal cyclohexylimine, the cleavage of the imine unit was easy.[6] Thus, we speculated that the corresponding aldehydes could be prepared from a chiral imine easier than SAMP-hydrazone. Thus we investigated the use of (4*S*,5*S*)-5-amino-2,2-dimethyl-1,3-dioxane ((4*S*,5*S*)-ADPD, **2**)[7] as a chiral



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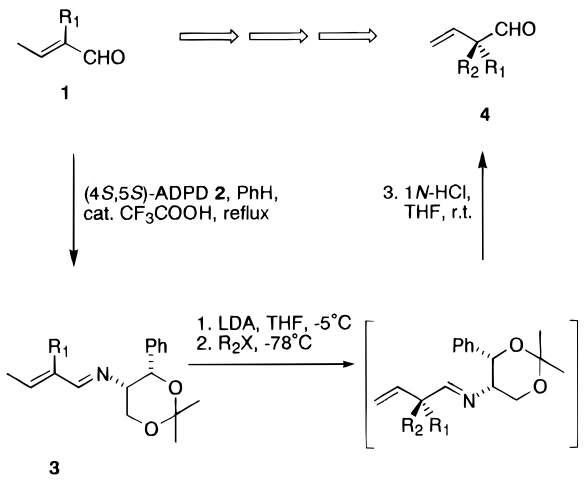
auxiliary and herein describe the synthesis of chiral 2,2-dialkyl-3-butenals **4** that have two different alkyl groups and vinyl group at the α-position by diastereoselective alkylation of 2-alkyl-2-butenal (4*S*,5*S*)-ADPD-imines **3** (Scheme 1).

Scheme 1



α-Alkyl-α,*β*-unsaturated aldehyde (4*S*,5*S*)-ADPD-imines **3** were conveniently prepared from α-alkyl-α,*β*-unsaturated aldehydes such as 2-methyl-2-butenal (**1a**) or 2-ethyl-2-butenal (**1b**) and (4*S*,5*S*)-5-amino-2,2-dimethyl-1,3-dioxane (**2**) using trifluoroacetic acid as a catalyst in 85% (**3a**) and 86% (**3b**) yields.

After deprotonation with lithium diisopropylamide (LDA) at −5 °C and alkylation with a variety of alkyl halides such as benzyl bromide, prenyl bromide, 1-iodopentane, and 1-bromononane at −78 °C, α-alkylated imines were hydrolyzed by 1 N hydrochloric acid. After purification by flash column chromatography, the chiral aldehydes **4** accompanied by double-bond migration were obtained in acceptable to good yields and enantiomeric excesses (Table 1).

The enantiomeric excesses of the aldehydes **4** are based on the determination of the corresponding diastereomeric excesses of SAMP-hydrazones **5**[8] (Scheme 2). The SAMP-hydrazones **5** were prepared from aldehydes **4** and 2 equiv of SAMP. This reaction was monitored by TLC. Determination of the corresponding diastereomeric excesses of **5** by gas chromatography was accomplished by employing cyclodextrin derivative phases[9] or by ^{13}C NMR spectra after purification by TLC or column chromatography.

(1) Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922.
(2) O'Hanlan, P. J.; Rogers, N. H. *Tetrahedron* **1987**, *43*, 2165.
(3) Sucrow, W.; Polyzou, P.; Slopianka, M.; Snatzke, G. *Tetrahedron Lett.* **1971**, 3237.
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(5) Mino, T.; Takagi, K.; Yamashita, M. *Synlett* **1996**, 645.
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(8) For comparsion, 1:1 mixture of diastereomer of SAMP-hydrazones **5** were prepared from SAMP and (±)-2,2-dialkyl-3-butenals which were obtained by alkylation of 2-alkyl-2-butenal dimethylhdrazones.[9]
(9) Mino, T.; Fukui, S.; Yamashita, M. *J. Org. Chem.* **1997**, *62*, 734.

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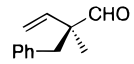
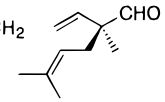
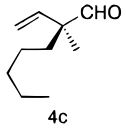
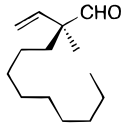
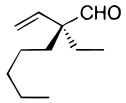
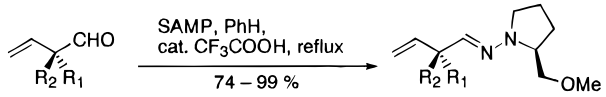
Table 1. Diastereoselective Alkylation of (4S,5S)-ADPD-imine 3

Entry	R^1	R^2	4	ee / %[a]	Yield / %[b]
1	Me	$PhCH_2$	 4a	40 (S)	69
2	Me	$Me_2C{=}CHCH_2$	 4b	61	42
3	Me	*n*-Pen	 4c	81	78
4	Me	*n*-Non	 4d	76	75
5	Et	*n*-Pen	 4e	63[c]	56

[a] Determined by GLC analysis with chiral column after the reaction of the corresponding aldehydes 4 with SAMP and measured as de value except **4e**. [b] Isolated yields. [c] Determined by 13C NMR analysis after the reaction of the corresponding aldehydes **4e** with SAMP and measured as de value.

Scheme 2

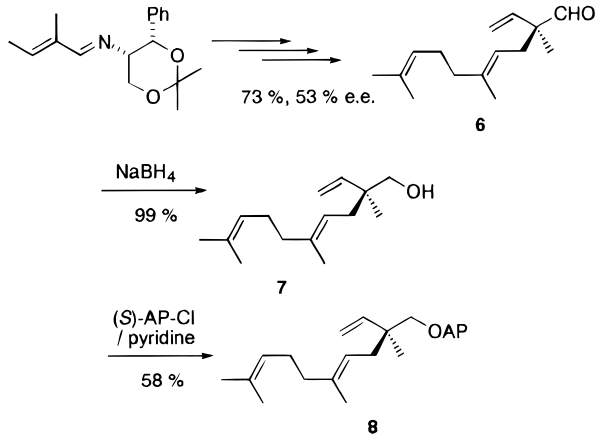


4 **5**

The absolute configuration at a quaternary carbon was assigned by the comparison with the retention time of GLC of the SAMP-hydrazones **5** which were prepared previously in our laboratory.[10]

Although (*E*)-2,5,9-trimethyl-2-vinyl-4,8-decadienal (**6**) had been identified as a sesquiterpene of a beefsteak plant 10 years ago,[11] the absolute configuration of the natural compound has not been determined. Thus using this alkylation, the (+)-(*E*)-aldehyde **6** was enantioselectively synthesized was conducted. After deprotonation of 2-methyl-2-butenal (4*S*,5*S*)-ADPD-imine (**3a**), alkylation with geranyl chloride and hydrolysis, the (+)-(*E*)-aldehyde **6**[12] was obtained in 73% yield and 53%ee. In this case, the enantiomeric excess of the aldehyde **6** could not be determined by the corresponding diastereomeric excess of SAMP-hydrazone by gas chromatography employing cyclodextrin derivative phases or by ^{13}C NMR spectra. Thus the enantiomeric excess of **6** was determined by ^1H and ^{13}C NMR spectra after derivation of the corresponding alcohol **7** to AP-ester **8**[13] by the reaction with (*S*)-2-acetoxypropionyl chloride[14] as shown in Scheme 3.

Scheme 3



In conclusion, we found that (4*S*,5*S*)-ADPD-imine **3** which has no α-hydrogen to be alkylated at the α-position by various alkyl halides accompanied by double bond migration to give 2,2-dialkyl-3-butenals (*S*)-**4** and **6** of good enantiomeric purity.

Experimental Section

General Procedures. ^1H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were taken in the $CDCl_3$ solvent and recorded in parts per million (ppm, δ) downfield from internal tetramethylsilane (Me_4Si). Column chromatography was performed on silica gel 60 (230−400 mesh), and thin-layer chromatography (TLC) was performed on silica gel 60 plates F_{254}. THF was dried and deoxygenated by distillation from potassium benzophenone under an argon atmosphere just before use. Benzene was purified by distillation over $CaCl_2$. Diisopropylamine was dried by distillation from potassium hydroxide. *n*-Butyllithium as a *ca.* 1.6 M hexane solution was titrated with *sec*-butyl alcohol using *o*-phenanthroline as an indicator just before use. The other organic compounds were commercial products of the highest available purity.

General Procedure for the Preparation of (4*S*,5*S*)-ADPD-imines 3a and 3b. In a flask equipped with a trap to remove water, a mixture of aldehyde (25 mmol), (4*S*,5*S*)-ADPD (25 mmol, 4.8 mL), trifluoroacetic acid (0.05 mL), and benzene (50 mL) was added under an argon atmosphere. The mixture was heated under reflux for 5 h and then cooled to room temperature. The reaction mixture was diluted with ether and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator.

2-Methyl-2-butenal (4*S*,5*S*)-ADPD-imine (3a): $[\alpha]^{19}_D$ = +161.3 (*c* 1.15, $CHCl_3$); IR (Nujol) 1640 (C=N) cm^{-1}; ^1H NMR δ 1.55−1.62 (m, 6H), 1.72−1.76 (m, 6H), 3.31−3.32 (m, 1H), 3.86−3.90 (m, 1H), 4.33−4.38 (m, 1H), 5.23 (d, *J* = 2.9 Hz, 1H), 5.64−5.69 (m, 1H), 7.15−7.38 (m, 5H), 7.44 (s, 1H); MS *m*/*z* 274 (M^+ + 1, 0.3). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.60; H, 8.49; N, 5.05. mp 81−83 °C.

2-Ethyl-2-butenal (4*S*,5*S*)-ADPD-imine (3b): $[\alpha]^{20}_D$ = +134.8 (*c* 1.15, $CHCl_3$); IR (neat) 1635 (C=N) cm^{-1}; ^1H NMR δ 0.81 (t, 6.9 Hz, 3H), 1.54−1.60 (m, 6H), 1.71 (d, *J* = 6.9 Hz, 3H), 2.16−2.21 (m, 1H), 2.35−2.40 (m, 1H), 3.32 (d, *J* = 2.9 Hz, 1H), 3.82−3.89 (m, 1H), 4.28−4.33 (m, 1H), 5.22 (d, *J* = 2.9 Hz, 1H), 5.59 (q, *J* = 6.9 Hz, 1H), 7.15−7.31 (m, 5H), 7.35

(10) Chrompack CP-cyclodextrin-β-236-M-19 column, 0.25 mm i.d. × 50 m.

(11) Uji, Y.; Toyoda, T.; Muraki, S. 31st Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Kyoto, September 1987; Abstr. No. 1I02.

(12) The synthesis of (±)-**6** has been reported: Yamashita, M.; Matsumiya, K.; Nakano, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1759.

(13) For comparison, a 1:1 mixture of diastereomer of AP-ester **8** was prepared from APCl and (±)-**7** which was obtained by alkylation of 2-methyl-2-butenal dimethylhdrazones and the subsequent reduction.

(14) Doolittle, R. E.; Heath, R. R. *J. Org. Chem.* **1984**, *49*, 5041.

(s, 1H); MS *m*/*z* 288 ($M^+ + 1$, 3). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.23; H, 8.77; N, 4.87. Found: C, 75.37; H, 8.86; N, 4.77.

General Procedure for the Synthesis of Aldehydes 4 and 6. To a solution of diisopropylamine (3.1 mmol, 0.41 mL) in THF (2 mL) in a dried reaction flask was added dropwise with stirring *n*-butyllithium in hexane (3.2 mmol, 2.04 mL) at −5 °C under an argon atmosphere. After 0.5 h, 2-alkyl-2-butenal (4*S*,5*S*)-ADPD-imines **3** (3.0 mmol) was added at −78 °C. After the solution was stirred for 1 h at the same temperature, alkyl halide (3.0 mmol) was added, and stirring was continued for 20 h at room temperature. The reaction mixture was quenched with water (25 mL), and THF (40 mL) and aqueous 2 N HCl (25 mL) were added. After stirring for 5 h, the reaction mixture was diluted with water and ether, washed with brine, and dried over $MgSO_4$. Removal of the solvents and column chromatography gave the pure aldehydes **4** and **6**.

2-Benzyl-2-methyl-3-butenal (4a): $[\alpha]^{24}_D = +22.6$ (*c* 4.2, ether) (40% ee); IR (neat) 1725 (C═O) cm^{-1}; ^1H NMR δ 1.13 (s, 3H), 2.88 (d, J = 13.4 Hz, 1H), 2.97 (d, J = 13.4 Hz, 1H), 5.09 (d, J = 17.7 Hz, 1H), 5.28 (d, J = 10.7 Hz, 1H), 5.86 (dd, J = 10.7 and 17.7 Hz, 1H), 7.09−7.28 (m, 5H), 9.51 (s, 1H); ^{13}C NMR δ 17.80, 42.00, 53.75, 117.11, 126.58, 128.07, 130.37, 136.46, 138.45, 202.46; MS *m*/*z* 174 (M^+, 2).

2,5-Dimethyl-2-vinyl-4-hexenal (4b): $[\alpha]^{25.5}_D = +25.7$ (*c* 0.86, $CHCl_3$) (61% ee); IR (neat) 1715 (C═O) cm^{-1}; ^1H NMR δ 1.15 (s, 3H), 1.61 (s, 3H), 1.70 (d, 1.2 Hz, 3H), 2.24−2.37 (m, 2H), 5.02−5.06 (m, 1H), 5.12 (dd, J = 0.9 and 17.7 Hz, 1H), 5.26 (dd, J = 0.9 and 11.0 Hz, 1H), 5.82 (dd, J = 11.0 and 17.7 Hz, 1H), 9.42 (s, 1H); ^{13}C NMR δ 17.84, 17.95, 25.93, 34.12, 53.26, 116.57, 118.28, 134.95, 138.75, 202.96; MS *m*/*z* 152 (M^+, 3).

2-Methyl-2-vinylheptanal (4c): $[\alpha]^{24.5}_D = +22.9$ (*c* 1.15, $CHCl_3$) (81% ee); IR (neat) 1735 (C═O) cm^{-1}; ^1H NMR δ 0.88 (t, 7.0 Hz, 3H), 1.16 (s, 3H), 1.18−1.31 (m, 6H), 1.55−1.60 (m, 2H), 5.11 (d, 17.7 Hz, 1H), 5.22 (d, 10.7 Hz, 1H), 5.80 (dd, 10.7 and 17.7 Hz, 1H), 9.39 (s, 1H); ^{13}C NMR δ 14.00, 17.67, 22.48, 23.56, 32.35, 35.50, 52.79, 116.43, 138.95, 203.05; MS *m*/*z* 125 (M^+ − CHO, 18); HRMS *m*/*z* (M^+ − CHO) calcd for C_9H_{17} 125.1326, Found 125.1319.

2-Methyl-2-vinylundecanal (4d): $[\alpha]^{26}_D = +15.9$ (*c* 1.0, $CHCl_3$) (76% ee); IR (neat) 1735 (C═O) cm^{-1}; ^1H NMR δ 0.88 (t, J = 6.9 Hz, 3H), 1.16 (s, 3H), 1.26 (br, 14H), 1.55−1.59 (m, 2H), 5.11 (d, J = 17.7 Hz, 1H), 5.26 (d, J = 11.0 Hz, 1H), 5.79 (dd, J = 11.0 and 17.7 Hz, 1H), 9.39 (s, 1H); ^{13}C NMR δ 14.10, 17.67, 22.68, 23.90, 29.30, 29.54, 30.19, 31.88, 35.54, 52.78, 116.41, 138.96, 203.01; MS *m*/*z* 210 (M^+, 0.01); Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.81; H, 12.40.

2-Ethyl-2-vinylheptanal (4e): $[\alpha]^{24}_D = -4.68$ (*c* 1.28, ether) (63% ee); IR (neat) 1745 (C═O) cm^{-1}; ^1H NMR δ 0.82 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H), 1.15−1.33 (m, 6H), 1.57−1.72 (m, 4H), 5.11 (d, J = 17.7 Hz, 1H), 5.32 (d, J = 11.0 Hz, 1H), 5.72 (dd, J = 11.0 and 17.7 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR δ 8.13, 14.01, 22.49, 23.36, 25.20, 32.16, 32.45, 56.25, 117.29, 137.95, 203.67; MS *m*/*z* 139 (M^+ − CHO, 10).

(*E*)-2,5,9-Trimethyl-2-vinyl-4,8-decadienal (6): $[\alpha]^{24.5}_D = +11.4$ (*c* 4.2, $CHCl_3$) (53% ee); IR (neat) 1730 (C═O) cm^{-1}; ^1H NMR δ 1.15 (s, 3H), 1.59 (s, 3H), 1.60 (s, 3H), 1.67 (s, 3H), 2.00−2.07 (m, 4H), 2.30 (dd, J = 7.3 and 14.0 Hz, 1H), 2.32 (dd, J = 7.3 and 14.0 Hz, 1H), 5.03−5.07 (m, 2H), 5.12 (d, J = 18.3 Hz, 1H), 5.26 (d, J = 11.0 Hz, 1H), 5.82 (dd, J = 11.0 and 18.3 Hz, 1H), 9.42 (s, 1H); ^{13}C NMR δ 16.22, 17.69, 17.73, 25.72, 26.47, 33.99, 39.89, 53.28, 116.54, 118.34, 124.12, 131.46, 138.44, 138.72, 202.94; MS *m*/*z* 220 (M^+, 5).

Reduction of Aldehyde 6. To a solution of aldehyde **6** (0.555 mmol, 0.122 g) in 5.0 mL of EtOH was added a solution of sodium borohydride (1.0 mmol, 0.04 g) in 1.0 mL of EtOH at room temperature. After 20 h, the reaction mixture was quenched with aqueous 2 N HCl and diluted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography to give (−)-(*E*)-2,5,9-trimethyl-2-vinyl-4,8-decadienol (**7**) (0.546 mmol, 0.121 g, 99%): $[\alpha]^{23}_D = -4.87$ (*c* 0.62, ether); IR (neat) 3400 (OH) cm^{-1}; ^1H NMR δ 0.99 (s, 3H), 1.49 (s, 3H), 1.60 (s, 6H), 1.68 (d, J = 1.2 Hz, 3H), 2.02−2.10 (m, 6H), 3.36 (d, J = 10.7 Hz, 1H), 3.41 (d, J = 10.7 Hz, 1H), 5.04−5.17 (m, 4H), 5.77 (dd, J = 10.7 and 17.4 Hz, 1H); ^{13}C NMR δ 16.17, 17.69, 20.08, 25.73, 26.57, 35.33, 40.00, 42.93, 69.73, 114.28, 119.95, 124.31, 131.38, 137.23, 144.14; MS *m*/*z* 222 (M^+, 0.8).

Preparation of Ester 8. To a solution of alcohol **7** (0.4 mmol, 0.089 g) in 2.0 mL of pyridine was added (*S*)-(−)-2-acetoxypropionyl chloride (0.6 mmol, 0.09 g) at 0°C. The reaction was monitored by TLC. After 3 h, the reaction mixture was quenched with aqueous 2 N HCl and diluted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography to give (−)-(*E*)-2,5,9-trimethyl-2-vinyl-4,8-decadienyl AP-ester (**8**) (0.30 mmol, 0.10 g, 58%): $[\alpha]^{23}_D = -26.1$ (*c* 0.58, Ether); IR (neat) 1760 (C═O) cm^{-1}; ^1H NMR δ 1.00−1.02 (m, 3H), 1.47−1.50 (m, 3H), 1.59 (s, 3H), 1.60 (s, 3H), 1.67 (s, 3H), 1.95−2.13 (m, 6H), 2.12 (s, 3H), 3.83−3.94 (m, 1H), 3.99−4.07 (m, 1H), 4.97−5.14 (m, 5H), 5.75 (dd, J = 11.0 and 17.6 Hz, 1H); ^{13}C NMR (major diastereomer) δ 16.16, 17.03, 17.70, 20.58, 20.67, 25.72, 26.54, 35.48, 39.99, 40.96, 68.57, 70.94, 113.49, 119.32, 124.26, 131.41, 137.79, 143.10, 170.28, 170.73; MS *m*/*z* 336 (M^+, 1.4).

Supporting Information Available: ^1H NMR spectra of **4a**−**c**, **4e**, **6**, **7**, and **8** and ^{13}C NMR spectra of **4e**, **6**, **7**, and **8** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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