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Double Asymmetric Induction in Organocatalyzed Aldol Reactions: Total Synthesis of (+)-2-*epi*-Hyacinthacine A_2 and (–)-3-*epi*-Hyacinthacine A_1

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The stereodivergent synthesis of two hyacinthacine analogues, which relies on an organocatalyzed aldol addition, is described. The aldol addition of dioxanone to an α-*N*-carbobenzyloxy-substituted chiral aldehyde, promoted by both (*R*)- and (*S*)-proline, proceeds in reasonable yields with acceptable diastereomeric ratios. The success of the reaction may be due to the use of an acyclic aldehyde acceptor, which allows reagent control of the stereochemical outcome of the key aldolization step in both the matched and mismatched cases.

Introduction

Reactions of chiral reagents with chiral substrates create the phenomenon of double asymmetric synthesis,[1] in which the stereochemical preferences of the substrate and the reagent can mutually reinforce (matched selectivity) or weaken (mismatched selectivity) each other. In principle, it is desirable that the stereochemical outcome of such reactions is determined by the reagent, for reasons of predictability and generality. The aldol reaction is among the most important methods for the formation of carbon–carbon bonds,[2] and powerful reagents have been developed that allow the stereochemical outcome of the reaction to be controlled even in cases of mismatched selectivity with stereochemically highly biased substrates.[3] However, in the rapidly developing field of organocatalysis,[4] the phenomenon of double asymmetric synthesis has not been systematically investigated. Examples are known in which chiral aldehydes are used as acceptors in aldolization reactions promoted by chiral organocatalysts.[5] Thus, the (*S*)-proline-catalyzed aldol addition of dioxanone to (*S*)-configured α-branched aldehydes offers efficient entry to a range of carbohydrate derivatives; however, in mismatched cases, the (*R*)-proline-catalyzed reaction afforded aldol products with yields lower than 40%.[6] In another study, both combinations gave the desired products in good yields with high diastereomeric excess (*de*) and enantiomeric excess (*ee*) values.[7] Proline-catalyzed aldolization reactions of dioxanone were also applied in the synthesis of azasugars by using α-azidoaldehydes as acceptors. In all of the reported examples, matched cases afforded the desired products in high yields with high selectivities. However, only one mismatched combination produced the aldol product in reasonable yield with acceptable (5:1) diastereoselectivity, whereas the other mismatched reactions were sluggish.[8] These results were also rationalized by calculations.[9]

Results and Discussion

We set out to further investigate stereodivergent routes to azasugars on the basis of organocatalysis. Our synthetic targets were analogues of hyacinthacine, which are a class of azasugars that has attracted considerable attention from the chemical community as a result of their strong inhibitory activity exerted upon enzymes involved in carbohydrate processing.[10] The synthetic challenge of these compounds is the installation of four contiguous stereocenters into a bicyclic core.[11–14] According to our retrosynthetic analysis, represented in Scheme 1, the stereogenic center at C-3 should be introduced in the reductive amination step, C-1 and C-2 should be created in the aldol reaction, whereas C-7a should be imported from the chiral precursor, glutamic acid.

Carbobenzyloxy (Cbz)-protected aldehyde **1** was prepared according to the procedure previously described for the *N*-*tert*-butoxycarbonyl (Boc) analogue.[15] The (*S*)-proline-catalyzed aldol addition of dioxanone to aldehyde **1** produced aldol adduct **2** as the major product, along with a minor amount of diastereoisomeric aldol **7** (70%; diastereoisomeric ratio (*dr*) = 6:1 for **2**/**7** and the diastereoisomers were separable by column chromatography; Scheme 2). Interestingly, a peak corresponding to a carb-

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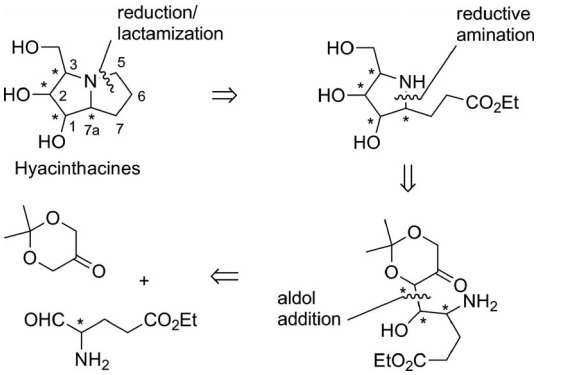
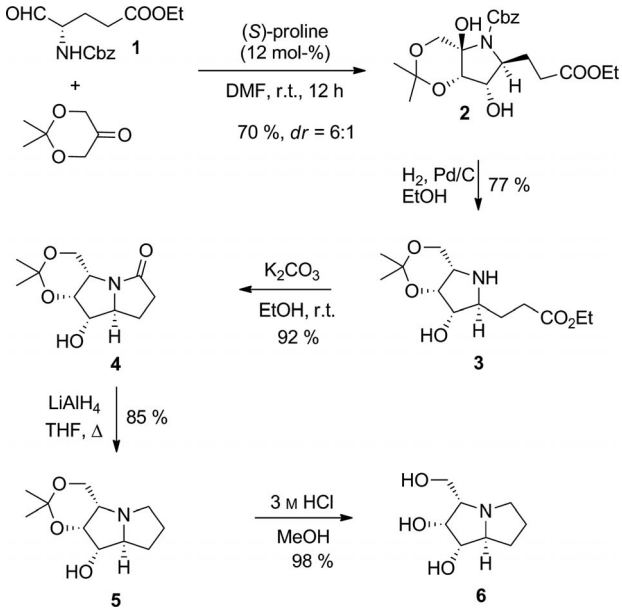


Scheme 1. Retrosynthetic analysis of hyacinthacines on the basis of organocatalyzed aldol addition.

onyl group (in the major diastereoisomer) could not be observed in ^{13}C NMR spectrum, whereas a peak at δ = 86.6 ppm was present; this indicated that the product assumed the cyclic, hemiaminal form, as confirmed by single-crystal X-ray diffraction analysis (Figure 1).[16] Reductive dehydroxylation of **2** proceeded without event and afforded desired pyrrolidine derivative **3** as a single isomer in 77% yield. Upon exposure to ethanolic potassium carbonate, **3** was converted into tricyclic lactam **4** (92%), and its stereochemical integrity was confirmed by X-ray analysis (for the crystal structure of **4**, see the Supporting Information). Reduction of lactam **4** with lithium aluminum hydride (85%) followed by acidic deprotection (98%) gave desired *ent*-2-*epi*-hyacinthacine A_2 (**6**), and its spectral and physical data were consistent with those previously reported {$[\alpha]_D^{20}$ = +32.0 (*c* = 0.65, MeOH), ref.[14b] $[\alpha]_D^{20}$ = +32.0 (*c* = 0.2, MeOH); m.p. 165–167 °C, corrected;[17] ref.[14b] m.p. 169–171 °C}.



Scheme 2. Synthesis of *ent*-2-*epi*-hyacinthacine A_2 (**6**).

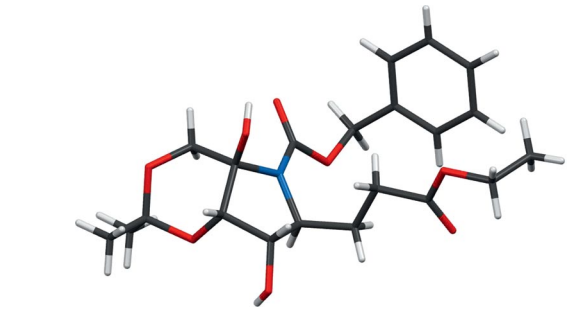
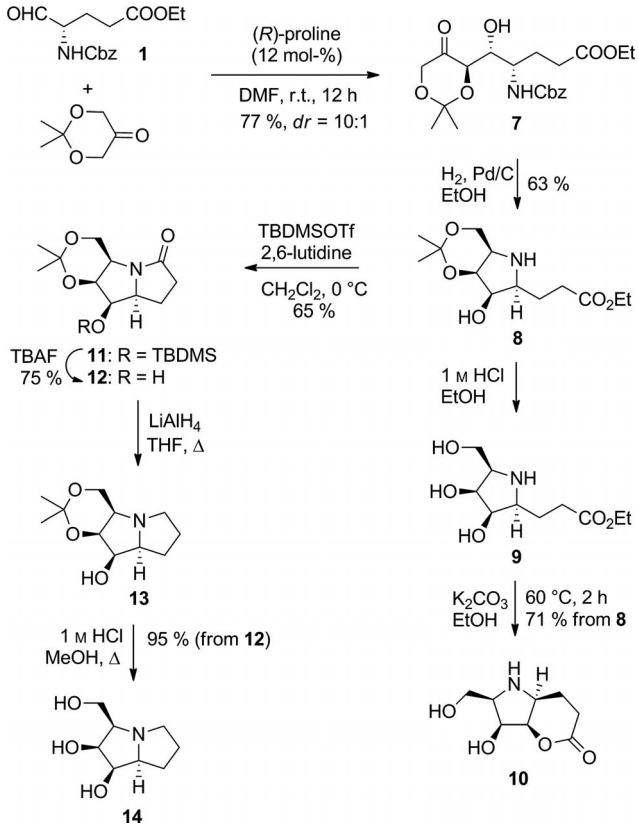


Figure 1. Aldol **2** in its hemiaminal form.

Next, we started a synthetic sequence leading to *ent*-3-*epi*-hyacinthacine A_1 (Scheme 3). The reaction of dioxanone with aldehyde **1** catalyzed by (*R*)-proline afforded aldol adduct **7** in 77% yield with 10:1 *dr*; the higher yield and stereoselectivity indicate that this is the matched case. Major aldol product **7** did not tautomerize into the hemiaminal form. Reductive amination with aldol **7** proceeded as before to afford pyrrolidine derivative **8** in 63% yield; however, this latter compound was reluctant to undergo lactamization and instead underwent ester hydrolysis. Attempts to facilitate lactamization by inverting the order of events, that is, by effecting the deprotection first, were not fruitful, as compound **9** underwent lactonization to **10** preferentially to lactamization. Protection of the C-1 hydroxy group in **8** with *tert*-butyldimethylsilyl triflate (TBDMSOTf) brought about spontaneous lactamization



Scheme 3. Synthesis of *ent*-3-*epi*-hyacinthacine A_1 (**14**).

(75%); to the best of our knowledge, silyl triflate promoted cyclization of amino esters is without literature precedent. The absolute configuration of lactam **12** was confirmed by X-ray analysis (for the crystal structure of **12**, see the Supporting Information). Reduction of lactam **12** with lithium aluminum hydride gave tricyclic amino alcohol **13**, which upon treatment with aqueous HCl was converted into the target molecule, *ent*-3-*epi*-hyacinthacine A_1 (**14**), as confirmed by its spectroscopic data, which are fully consistent with the previously described data. However, there is a discrepancy between the literature values for the optical rotation of **14**; our results are more consistent with those given in ref.[12a] {$[\alpha]_D^{20}$ = –6.8 (*c* = 0.32, H_2O), ref.[12a,18] $[\alpha]_D^{20}$ = +3.4 (*c* = 0.32, H_2O), ref.[13g] $[\alpha]_D^{20}$ = –1.0 (*c* = 0.6, MeOH)}.

Conclusions

To summarize, the stereodivergent synthesis of two *epi*-hyacinthacine analogues was achieved on the basis of aldolization reactions of dioxanone with a chiral aldehyde catalyzed by both enantiomers of proline. Both matched and mismatched combinations of reagents gave good results in terms of yield and stereoselectivity. Thus, it appears that in organocatalyzed double asymmetric aldol addition reactions, the use of acyclic aldehyde acceptors offers better chances for reagent control to be achieved.[19]

Experimental Section

General: All chromatographic separations were performed on silica gel, 10–18, 60 Å (dry-flash), 100–200 60 Å (column chromatography), ICN Biomedicals, and ion-exchange column chromatography (acidic resin DOWEX 50WX8-100). Standard techniques were used for the purification of the reagents and solvents. Petroleum ether (PE) refers to the fraction boiling at 70–72 °C. NMR spectra were recorded with a Bruker Avance III 500 (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz). Chemical shifts are expressed in ppm (δ) using tetramethylsilane as the internal standard. IR spectra were recorded with a Nicolet 6700 FT instrument. Mass spectra were obtained with an Agilent Technologies 6210 TOF LC–MS instrument (LC: series 1200) and LTQ Orbitrap XL hybrid FTMS (Thermo Scientific). Microanalyses were performed by using a Vario EL III instrument CHNOS Elementar Analyzer, Elementar Analysensysteme GmbH, Hanau, Germany. Melting points were determined with a Kofler hot-stage and Electrothermal apparatus and are uncorrected, unless otherwise stated. Optical rotation was determined with a Rudolph Research Analytical AUTOPOL IV Automatic Polarimeter. Diffraction data were collected with an Oxford Diffraction KM4 four-circle goniometer equipped with a Sapphire CCD detector.

Aldol Addition Catalyzed by (*S*)-Proline to Afford (4a*R*,6*S*,7*S*,7a*S*)-Benzyl 6-(3-Ethoxy-3-oxopropyl)-4a,7-dihydroxy-2,2-dimethyltetrahydro[1,3]dioxino[5,4-*b*]pyrrole-5(6*H*)-carboxylate (2): A solution of dioxanone (436.0 mg, 3.35 mmol), aldehyde **1** (674.6 mg, 2.30 mmol), and (*S*)-proline (49.6 mg, 0.43 mmol) in DMF was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extract was washed with water, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO_2; petroleum ether/ethyl acetate, 6:4) afforded title aminal **2** (575.0 mg, 59%) followed by diastereoisomeric aldol **7** (97.4 mg, 10%). Data for **2**: White crystals, m.p. 99–101 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 65 °C): δ = 7.41–7.29 (m, 5 H), 5.85 (s, 1 H), 5.10 (dd, *J* = 12.5, 8.0 Hz, 2 H), 4.61 (br. d, *J* = 7.5 Hz, 1 H), 4.35–4.15 (m, 1 H), 4.11–4.04 (m, 1 H), 4.05 (q, *J* = 7.0 Hz, 2 H), 3.78 (d, *J* = 4.5 Hz, 1 H), 3.76 (d, *J* = 12.0 Hz, 1 H), 3.63 (td, *J* = 7.7, 2.7 Hz, 1 H), 2.37–2.22 (m, 2 H), 2.20–2.09 (m, 1 H), 2.04–1.96 (m, 1 H), 1.38 (s, 3 H), 1.27 (s, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]-DMSO, 65 °C): δ = 172.4 (C), 153.3 (C), 136.4 (C), 127.9 (CH), 127.4 (CH), 127.4 (CH), 98.4 (C), 86.6 (C), 75.5 (CH_2), 71.0 (CH), 65.7 (CH_2), 64.9 (CH), 61.6 (CH), 59.3 (CH_2), 28.7 (CH_2), 26.1 (CH_2), 25.9 (CH_3), 20.9 (CH_3), 13.7 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3435, 2928, 1730, 1702, 1453, 1413, 1378, 1337, 1220, 1078 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{29}NO_8$ [M + Na]$^+$ 446.1785; found 446.1783. $C_{21}H_{29}NO_8$ (423.46): calcd. C 59.56, H 6.90, N 3.31; found C 59.35, H 6.96, N 3.19. $[\alpha]_D^{20}$ = +5.4 (*c* = 1.00, $CHCl_3$).

Reductive Dehydroxylation of 2 to Afford Ethyl 3-[(4a*S*,6*S*,7*S*,7a*R*)-7-Hydroxy-2,2-dimethylhexahydro[1,3]dioxino[5,4-*b*]pyrrol-6-yl]-propanoate (3): A mixture of aldol **2** (240.0 mg, 0.57 mmol) and Pd/C (10%, 75.0 mg, 0.07 mmol) in ethanol (48.0 mL) was stirred overnight under a hydrogen atmosphere (5 atm). The mixture was filtered and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (SiO_2; dichloromethane/methanol, 8:2) afforded **3** (119.3 mg, 77%) as a colorless viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.17 (br. t, *J* = 4.0 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.00 (dd, *J* = 12.4, 4.2 Hz, 1 H), 3.76 (dd, *J* = 8.0, 4.4 Hz, 1 H), 3.64 (dd, *J* = 12.4, 3.7 Hz, 1 H), 3.16–3.09 (m, 2 H), 2.73 (br. s, 2 H), 2.47 (ddd, *J* = 8.1, 6.8, 5.4 Hz, 2 H), 2.03–1.96 (m, 1 H), 1.79–1.72 (m, 1 H), 1.43 (s, 3 H), 1.39 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.6 (C), 98.3 (C), 79.9 (CH), 70.9 (CH), 62.3 (CH), 60.8 (CH_2), 60.3 (CH_2), 52.9 (CH), 31.6 (CH_2), 29.6 (CH_2), 28.1 (CH_3), 20.1 (CH_3), 14.2 (CH_3) ppm. IR (film): $\tilde{\nu}$ 3333, 2987, 2934, 1731, 1446, 1377, 1343, 1271, 1226, 1197, 1168, 1136, 1059, 949 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{23}NO_5$ [M + H]$^+$ 274.1649; found 274.1645. $[\alpha]_D^{20}$ = –39.3 (*c* = 1.03, $CHCl_3$).

(4a*S*,8a*S*,9*S*,9a*R*)-9-Hydroxy-2,2-dimethylhexahydro[1,3]dioxino-[4,5-*b*]pyrrolizin-6(7*H*)-one (4): A mixture of amine **3** (108.8 mg, 0.40 mmol), K_2CO_3 (249.0 mg, 1.80 mmol), and ethanol (4.5 mL) was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the crude product was purified by dry-flash chromatography (SiO_2; dichloromethane/methanol, 95:5) to give **4** (83.4 mg, 92%) as white crystals, m.p. 116–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.45 (t, *J* = 4.2 Hz, 1 H), 4.09–4.03 (m, 2 H), 3.88–3.83 (m, 2 H), 3.71–3.65 (m, 1 H), 2.78–2.70 (m, 1 H), 2.56 (br. d, *J* = 11.1 Hz, 1 H), 2.46–2.38 (m, 2 H), 1.99–1.90 (m, 1 H), 1.46 (s, 3 H), 1.42 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.5 (C), 98.7 (C), 78.0 (CH), 72.1 (CH), 64.3 (CH), 60.3 (CH_2), 50.8 (CH), 34.0 (CH_2), 27.3 (CH_3), 24.7 (CH_2), 20.7 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3411, 2990, 2939, 2889, 1677, 1457, 1403, 1381, 1334, 1278, 1238, 1202, 1170, 1141, 1108, 1080, 1046, 960, 903 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}NO_4$ [2M + H]$^+$ 455.2388; found 455.2376. $C_{11}H_{17}NO_4$ (227.26): calcd. C 58.14, H 7.54, N 6.16; found C 57.77, H 7.46, N 5.89. $[\alpha]_D^{20}$ = +105.7 (*c* = 1.53, $CHCl_3$).

(4a*S*,8a*S*,9*S*,9a*R*)-2,2-Dimethyloctahydro[1,3]dioxino[4,5-*b*]pyrrolizin-9-ol (5): To a solution of amide **4** (83.0 mg, 0.40 mmol) in freshly distilled, cold (0 °C) THF (10.0 mL) was added lithium aluminum hydride (40.0 mg, 0.90 mmol) in portions over 5 min. The reaction mixture was stirred for 5 min at 0 °C and then heated at 70 °C for

1 h. The reaction mixture was then cooled (0 °C) and quenched by the subsequent addition of water (80 μL), 10% aq. NaOH (80 μL), and water (240 μL). The resulting mixture was filtered, and the precipitate was washed with EtOAc. The combined organic extract was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (SiO_2; dichloromethane/methanol, 8:2) afforded **5** (66.3 mg, 85%) as a colorless viscous oil. ^{1}H NMR (500 MHz, CD_3OD): δ = 4.32 (t, J = 3.5 Hz, 1 H), 4.06 (dd, J = 12.6, 2.6 Hz, 1 H), 3.74–3.68 (m, 2 H), 3.48 (td, J = 8.5, 3.0 Hz, 1 H), 2.87 (dt, J = 11.0, 6.9 Hz, 1 H), 2.66–2.58 (m, 2 H), 1.99–1.89 (m, 1 H), 1.82–1.75 (m, 3 H), 1.46 (s, 3 H), 1.42 (s, 3 H) ppm. ^{13}C NMR (126 MHz, CD_3OD): δ = 99.1 (C), 79.8 (CH), 74.2 (CH), 69.7 (CH), 62.7 (CH_2), 62.3 (CH), 55.3 (CH_2), 31.3 (CH_2), 29.6 (CH_3), 25.8 (CH_2), 19.5 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3071, 2994, 2946, 2912, 2872, 2830, 1582, 1452, 1376, 1331, 1272, 1231, 1199, 1175, 1141, 1087, 1025, 955, 869 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{19}NO_3$ [M + H]$^+$ 214.1438; found 214.1428. $[\alpha]_D^{20}$ = +15.7 (c = 0.81, MeOH).

***ent*-2-*epi*-Hyacinthacine A$_2$ (6):** A solution of amine **5** (39.5 mg, 0.18 mmol) in methanol/3 M HCl (4.6 mL, v/v = 2:1) was stirred and heated to reflux for 2 h. After the volatiles were removed under reduced pressure, the residue was purified by ion-exchange column chromatography (acidic resin DOWEX 50WX8–100) to give **6** (31.3 mg, 98%) as white crystals, which were recrystallized from 2-propanol, m.p. 165–167 °C, corrected[17] (ref.[14b] m.p. 169–171 °C). ^{1}H NMR (500 MHz, D_2O): δ = 4.26 (t, J = 3.6 Hz, 1 H), 3.91 (dd, J = 8.6, 4.0 Hz, 1 H), 3.85 (dd, J = 11.0, 7.7 Hz, 1 H), 3.67 (dd, J = 11.0, 6.0 Hz, 1 H), 3.38 (td, J = 8.2, 3.7 Hz, 1 H), 2.94 (ddd, J = 7.7, 6.0, 3.3 Hz, 1 H), 2.88–2.83 (m, 1 H), 2.74–2.68 (m, 1 H), 1.98–1.73 (m, 4 H) ppm. ^{13}C NMR (126 MHz, D_2O): δ = 79.7 (CH), 76.2 (CH), 71.6 (CH), 69.6 (CH), 62.9 (CH_2), 57.0 (CH_2), 31.9 (CH_2), 27.2 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3399, 2966, 2923, 2872, 2709, 1739, 1573, 1460, 1361, 1320, 1260, 1205, 1159, 1123, 1085, 1048, 1011, 983, 916, 814 cm^{-1}. HRMS (ESI): calcd. for $C_8H_{15}NO_3$ [M + H]$^+$ 174.1125; found 174.1126. $[\alpha]_D^{20}$ = +32.0 (c = 0.65, MeOH) {ref.[14b] $[\alpha]_D^{20}$ = +32.0 (c = 0.20, MeOH)}.

Aldol Addition Catalyzed by (*R*)-Proline to Afford (4*S*,5*R*)-Ethyl 4-(Benzyloxycarbonylamino)-5-[(*R*)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl]-5-hydroxypentanoate (7): A solution of dioxanone (0.8 g, 6.15 mmol), aldehyde **1** (1.1 g, 3.72 mmol), and (*R*)-proline (82.0 mg, 0.71 mmol) in DMF (8.4 mL) was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extract was washed with water, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO_2; petroleum ether/ethyl acetate, 6:4) afforded title aldol **7** (1.1 g, 70%) as a yellow oil followed by diastereoisomeric aldol **2** (110.0 mg, 7%). Data for **7**: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.40–7.27 (m, 5 H), 6.64 (d, J = 9.5 Hz, 1 H), 5.04 (d, J = 6.5 Hz, 1 H), 5.00 (dd, J = 23.5, 12.5 Hz, 2 H) 4.27 (dd, J = 17.2, 1.1 Hz, 1 H), 4.17 (dd, J = 6.5, 1.0 Hz, 1 H), 4.05–3.99 (m, 3 H), 3.80–3.68 (m, 2 H), 2.26 (br. t, J = 7.7 Hz, 2 H), 1.70 (dd, J = 14.8, 7.3 Hz, 2 H), 1.31 (s, 3 H), 1.26 (s, 3 H), 1.16 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 208.3 (C), 172.6 (C), 156.0 (C), 137.2 (C), 128.3 (CH), 127.7 (CH), 127.6 (CH), 100.5 (C), 74.5 (CH), 69.5 (CH), 66.4 (CH_2), 65.2 (CH_2), 59.7 (CH_2), 50.8 (CH), 30.4 (CH_2), 27.1 (CH_2), 23.9 (CH_3), 22.9 (CH_3), 14.1 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3500, 3439, 3377, 3089, 3064, 3034, 2986, 2939, 2904, 1730, 1713, 1519, 1451, 1417, 1380, 1332, 1257, 1179, 1092, 1044, 949, 863 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{29}NO_8$ [M + H]$^+$ 424.1966; found 424.1961. $[\alpha]_D^{20}$ = +87.0 (c = 1.27, $CHCl_3$).

Reductive Amination of 7 to Afford Ethyl 3-[(4*aR*,6*S*,7*R*,7*aS*)-7-Hydroxy-2,2-dimethylhexahydro[1,3]dioxino[5,4-*b*]pyrrol-6-yl]propanoate (8): A mixture of aldol **7** (240.0 mg, 0.57 mmol) and Pd/C (10%, 82.0 mg, 0.08 mmol) in ethanol (46.0 mL) was stirred overnight under a hydrogen atmosphere (5 atm). The mixture was filtered and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (SiO_2; dichloromethane/methanol, 8:2) afforded **8** (97.6 mg, 63%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.33–4.28 (m, 2 H), 4.18–4.10 (m, 3 H), 3.81 (dd, J = 12.5, 3.5 Hz, 1 H), 3.72–3.45 (m, 2 H), 3.17 (dt, J = 8.6, 6.1 Hz, 1 H), 3.03 (dd, J = 7.3, 3.8, Hz, 1 H), 2.60–2.48 (m, 2 H), 2.11–2.03 (m, 1 H), 1.93–1.85 (m, 1 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.26 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.0 (C), 99.0 (C), 73.7 (CH), 70.6 (CH), 61.2 (CH), 60.6 (CH_2), 60.1 (CH_2), 53.9 (CH), 31.9 (CH_2), 28.2 (CH_3), 24.7 (CH_2), 20.1 (CH_3), 14.2 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3502, 2988, 2937, 1732, 1650, 1452, 1377, 1226, 1170, 1137, 1095, 1067, 946 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{23}NO_5$ [M + H]$^+$ 274.1649; found 274.1635. $[\alpha]_D^{20}$ = +10.9 (c = 1.16, $CHCl_3$).

(2*R*,3*S*,3*aR*,7*aS*)-3-Hydroxy-2-(hydroxymethyl)hexahydropyrano-[3,2-*b*]pyrrol-5(6*H*)-one (10): A solution of amine **8** (29.5 mg, 0.11 mmol) in ethanol/1.5 M HCl (6.0 mL, v/v = 2:1) was stirred for 2 h at room temperature. The solvent and the volatiles were removed under reduced pressure to give crude **9** (29.0 mg) as a pale yellow viscous oil, which was used further without purification. A mixture of crude **9** (29.0 mg, 0.12 mmol) and K_2CO_3 (64.0 mg, 0.46 mmol) in ethanol (1.2 mL) was heated to 66 °C for 2 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; dichloromethane/methanol, 8:2), to give **10** (14.4 mg, 71%) as white crystals, m.p. 148–152 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 4.49 (d, J = 4.0 Hz, 1 H), 4.06 (dd, J = 11.5, 2.5 Hz, 1 H), 3.86 (ddd, J = 9.6, 6.5, 3.0 Hz, 1 H), 3.73 (br. t, J = 3.5 Hz, 1 H), 3.71–3.67 (m, 1 H), 3.59 (dd, J = 11.6, 4.0 Hz, 1 H), 2.61–2.50 (m, 1 H), 2.31 (ddd, J = 16.5, 9.3, 0.9 Hz, 1 H), 2.14 (tt, J = 12.0, 9.5 Hz, 1 H), 1.92–1.83 (m, 1 H) ppm. ^{13}C NMR (126 MHz, CD_3OD): δ = 177.0 (C), 76.7 (CH), 70.3 (CH), 65.3 (CH), 59.6 (CH), 57.9 (CH_2), 35.6 (CH_2), 21.1 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3248, 2953, 2894, 1656, 1446, 1373, 1343, 1306, 1239, 1197, 1145, 1022, 981 cm^{-1}. HRMS (ESI): calcd. for $C_8H_{13}NO_4$ [M + H]$^+$ 188.0917; found 188.0913. $[\alpha]_D^{20}$ = +18.5 (c = 0.93, MeOH).

(4*aR*,8*aS*,9*R*,9*aS*)-9-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylhexahydro[1,3]dioxino[4,5-*b*]pyrrolizin-6(7*H*)-one (11): To a solution of amine **8** (200.0 mg, 0.73 mmol) in cold (0 °C) dichloromethane (1.2 mL) was added 2,6-lutidine (644.0 mg, 6.01 mmol) and TBDMSOTf (805.0 mg, 3.04 mmol) under an argon atmosphere. The reaction mixture was stirred for 30 min at room temperature, then diluted with dichloromethane, washed with aqueous saturated $NaHCO_3$, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; dichloromethane/methanol, 95:5), to give **11** (46.4 mg, 65%) as white crystals, m.p. 70–72 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.47 (dd, J = 10.5, 5.2 Hz, 1 H), 4.33 (dd, J = 7.5, 4.4 Hz, 1 H), 4.12 (dd, J = 4.3, 3.5 Hz, 1 H), 3.88 (t, J = 10.4 Hz, 1 H), 3.81 (td, J = 7.3, 3.3 Hz, 1 H), 3.67–3.59 (m, 1 H), 2.60–2.50 (m, 1 H), 2.45 (ddd, J = 16.8, 10.1, 3.0 Hz, 1 H), 2.24 (dtd, J = 12.5, 9.9, 7.2 Hz, 1 H), 1.93 (dddd, J = 12.5, 9.4, 7.6, 3.1 Hz, 1 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 0.92 (s, 9 H), 0.12 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.8 (C), 99.4 (C), 74.4 (CH), 71.2 (CH), 63.6 (CH), 59.2 (CH_2), 51.8 (CH), 34.4 (CH_2), 27.6 (CH_3), 25.8 (CH_3), 24.9 (CH_3), 18.8 (CH_2), 18.4 (C), –4.3 (CH_3), –5.2 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3503, 2987, 2954, 2932, 2891, 2857, 1688, 1466, 1418, 1375, 1297, 1253, 1219, 1140, 1051,

1027, 1010, 972 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{31}NO_4Si$ [M + H]$^+$ 342.2095; found 342.2095. $[\alpha]_D^{20}$ = +25.1 (*c* = 0.71, $CHCl_3$).

(4*aR*,8*aS*,9*R*,9*aS*)-9-Hydroxy-2,2-dimethylhexahydro[1,3]dioxino-[4,5-*b*]pyrrolizin-6(7*H*)-one (12): A solution of lactam **11** (46.4 mg, 0.14 mmol) and tetrabutylammonium fluoride (TBAF; 50.0 mg, 0.19 mmol) in freshly distilled THF (11.3 mL) was stirred for 1 h at room temperature. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2; dichloromethane/methanol, 95:5) to give **12** (22.3 mg, 75%) as white crystals, m.p. 110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.50 (dd, *J* = 11.3, 5.8 Hz, 1 H), 4.43 (dd, *J* = 7.1, 4.9 Hz, 1 H), 4.16–4.09 (m, 1 H), 3.92–3.79 (m, 2 H), 3.71–3.62 (m, 1 H), 3.00 (br. d, *J* = 1.2 Hz, 1 H), 2.64–2.44 (m, 2 H), 2.37 (dtd, *J* = 12.6, 9.8, 7.3 Hz, 1 H), 2.04–1.97 (m, 1 H), 1.42 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.9 (C), 100.1 (C), 73.6 (CH), 69.0 (CH), 63.7 (CH), 58.9 (CH_2), 52.1 (CH), 34.5 (CH_2), 26.2 (CH_3), 24.4 (CH_3), 18.2 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 3498, 2986, 2954, 2913, 1675, 1447, 1370, 1338, 1301, 1218, 1184, 1149, 1119, 1054, 1024, 876 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}NO_4$ [M + H]$^+$ 228.1230; found 228.1227. $[\alpha]_D^{20}$ = +9.8 (*c* = 0.83, $CHCl_3$).

***ent*-3-*epi*-Hyacinthacine A$_1$ (14):** To a cold (0 °C) solution of amide **12** (22.3 mg, 0.09 mmol) in freshly distilled THF (3.0 mL) was added lithium aluminum hydride (10.2 mg, 0.30 mmol) in portions over 5 min. The reaction mixture was stirred for 5 min at 0 °C and then heated to 70 °C for 1 h. After cooling to 0 °C, the reaction mixture was quenched by the sequential addition of water (20 μL), 10% NaOH (20 μL), and water (60 μL). The resulting mixture was filtered and concentrated under reduced pressure to give crude **13** (20.7 mg) as a pale yellow viscous oil, which was used further without purification. A solution of crude amine **13** (20.7 mg, 0.09 mmol) in methanol/1 M HCl (4.0 mL, v/v = 2:1) was heated to reflux for 2 h. After the volatiles were removed under reduced pressure, the residue was purified by ion-exchange column chromatography (acidic resin DOWEX 50WX8-100) to give **14** (16.8 mg, 95%) as a pale yellow viscous oil. ^{1}H NMR (500 MHz, CD_3OD): δ = 4.24–4.15 (m, 2 H), 3.95 (dd, *J* = 12.0, 5.5 Hz, 2 H), 3.91 (dd, *J* = 12.0, 7.0 Hz, 1 H), 3.73 (dd, *J* = 15.5, 7.6 Hz, 1 H), 3.33–3.29 (m, 2 H), 3.14–3.05 (m, 1 H), 2.22–2.10 (m, 1 H), 2.09–2.01 (m, 1 H), 1.85–1.74 (m, 2 H) ppm. ^{13}C NMR (126 MHz, CD_3OD): δ = 74.7 (CH), 72.1 (CH), 68.6 (CH), 65.6 (CH), 58.2 (CH_2), 50.3 (CH_2), 27.5 (CH_2), 26.1 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3358, 2924, 1651, 1504, 1457, 1340, 1139, 1038, 979, 729 cm^{-1}. HRMS (ESI): calcd. for $C_8H_{15}NO_3$ [M + H]$^+$ 174.1125; found 174.1122. $[\alpha]_D^{20}$ = –6.8 (*c* = 0.32, H_2O) {ref.[12a,18] $[\alpha]_D^{20}$ = +3.4 (*c* = 0.32, H_2O), ref.[13g] $[\alpha]_D^{20}$ = –1.0 (*c* = 0.6, MeOH)}.

CCDC-935825 (for **2**), -935822 (for **4**), and -935850 (for **12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedure and spectroscopic data for aldehyde **1**; ORTEP diagrams of compounds **2**, **4**, and **12**; copies of the ^{1}H NMR and ^{13}C NMR spectra for all compounds.

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[1] S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem.* **1985**, *97*, 1–31; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1–30.

[2] a) R. Mahrwald (Ed.), *Modern Aldol Reactions*, Wiley-VCH, Weinheim, Germany, **2004**, vols. 1 and 2; for review articles, see: b) C. Heathcock, in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, UK, **1991**, vol. 2, p. 133–179; c) C. Heathcock, in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, UK, **1991**, vol. 2, p. 181–238; d) B. M. Kim, S. F. Williams, S. Masamune, in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, UK, **1991**, vol. 2, p. 239–275; for a review article on catalytic enantioselective aldol reactions, see: e) E. M. Carreira, A. Fettes, C. Marti, *Org. React.* **2006**, *67*, 2–216.

[3] For representative examples, see: a) D. A. Evans, J. Bartoli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129; b) D. A. Evans, J. Bartoli, *Tetrahedron Lett.* **1982**, *23*, 807–810; c) S. Masamune, M. Hirama, S. Mori, Sk. A. Ali, D. S. Garvey, *J. Am. Chem. Soc.* **1981**, *103*, 1568–1571; d) for a tabular survey of aldol reactions of boron enolates with double asymmetric induction, see: C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 3–200.

[4] Books on organocatalysis: a) P. I. Dalko, *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley-VCH, Weinheim, Germany, **2007**; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis – From Biomimetic Concepts to Applications, in: Asymmetric Synthesis* Wiley-VCH, Weinheim, Germany, **2005**; review articles: c) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; d) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; e) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; f) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; g) B. List, J. W. Yang, *Science* **2006**, *313*, 1584–1586; h) J. Seagad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; i) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; j) a thematic issue of *Chem. Rev.* **2007**, *107*, No. 12 is dedicated to organocatalysis k) a thematic issue of *Acc. Chem. Res.* **2004**, *37* (No. 8) is dedicated to organocatalysis.

[5] Review article on enantioselective organocatalyzed aldol reactions: V. Bisai, A. Bisai, V. K. Singh, *Tetrahedron* **2012**, *68*, 4541–4580; however, no examples of double asymmetric reactions are provided.

[6] D. Enders, C. Grondal, *Angew. Chem.* **2005**, *117*, 1235–1238; *Angew. Chem. Int. Ed.* **2005**, *44*, 1210–1212.

[7] I. Ibrahem, W. Zou, Y. Xu, A. Cordova, *Adv. Synth. Catal.* **2006**, *348*, 211–222.

[8] F. Calderón, E. G. Doyagüez, A. F. Fernández-Mayoralas, *J. Org. Chem.* **2006**, *71*, 6258–6261.

[9] F. Calderón, E. G. Doyagüez, P. H.-Y. Cheong, A. Fernández-Mayoralas, K. N. Houk, *J. Org. Chem.* **2008**, *73*, 7916–7920.

[10] For selected review articles on iminosugars and their biological properties, see: a) B. G. Winchester, *Tetrahedron: Asymmetry* **2009**, *20*, 645–651; b) N. Asano, R. J. Nash, R. J. Molyneux, G. W. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; c) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265–295; d) J. R. Lidell, *Nat. Prod. Rep.* **2000**, *17*, 455–462.

[11] Review articles on the synthesis of iminosugars and bicyclic polyhydroxylated alkaloids: a) B. L. Stocker, E. M. Dangerfield, A. L. Win-Mason, G. W. Haslett, M. S. M. Timmer, *Eur. J. Org. Chem.* **2010**, 1615–1637; b) M. D. Lopez, J. Cobo, M. Nogueras, *Curr. Org. Chem.* **2008**, *12*, 718–750.

[12] Total syntheses of hyacinthacine A$_1$: a) L. Chabaud, Y. Landais, P. Renaud, *Org. Lett.* **2005**, *7*, 2587–2590; b) T. J. Donohoe, H. O. Sintim, J. Hollinshead, *J. Org. Chem.* **2005**, *70*, 7297–7304; c) I. Izquierdo, M.-T. Plaza, J. A. Tamayo, F. Sanchez-Cantalejo, *Eur. J. Org. Chem.* **2007**, 6078–6083; d) S. Chandrasekhar, B. B. Parida, C. Rambabu, *J. Org. Chem.* **2008**, *73*,

7826–7828; e) P. V. Reddy, A. Veyron, P. Koos, A. Bayle, A. E. Greene, P. Delair, *Org. Biomol. Chem.* **2008**, *6*, 1170–1172.
[13] Syntheses of hyacinthacine A_2: a) M. Royzen, M. T. Taylor, A. DeAngelis, J. M. Fox, *Chem. Sci.* **2011**, *2*, 2162–2165; b) X.-K. Liu, S. Qiu, Y.-G. Xiang, Y.-P. Ruan, X. Zheng, P.-Q. Huang, *J. Org. Chem.* **2011**, *76*, 4952–4963; c) C. Bonaccini, M. Chioccioli, C. Parmeggiani, F. Cardona, D. Lo Re, G. Soldaini, P. Vogel, C. Bello, A. Goti, P. Gratteri, *Eur. J. Org. Chem.* **2010**, 5574–5585; d) W.-J. Liu, J.-L. Ye, P.-Q. Huang, *Org. Biomol. Chem.* **2010**, *8*, 2085–2091; e) I. Delso, T. Tejero, A. Goti, P. Merino, *Tetrahedron* **2010**, *66*, 1220–1227; f) C. Ribes, E. Falomir, M. Carda, J. A. Marco, *Tetrahedron* **2009**, *65*, 6965–6971; g) J. Calveras, J. Casas, T. Parella, J. Joglar, P. Clapes, *Adv. Synth. Catal.* **2007**, *349*, 1661–1666; h) P. Dewi-Wulfing, S. Blechert, *Eur. J. Org. Chem.* **2006**, 1852–1856; i) S. Desvergnes, S. Py, Y. Vallée, *J. Org. Chem.* **2005**, *70*, 1459–1462; j) I. Izquierdo, M. T. Plaza, F. Franco, *Tetrahedron: Asymmetry* **2003**, *14*, 3933–3935; k) F. Cardona, E. Faggi, F. Liguori, M. Cacciarini, A. Goti, *Tetrahedron Lett.* **2003**, *44*, 2315–2318; l) L. Rambaud, P. Compain, O. R. Martin, *Tetrahedron: Asymmetry* **2001**, *12*, 1807–1809.
[14] Syntheses of hyacinthacine analogues: a) A. Rajender, J. P. Rao, B. V. Rao, *Eur. J. Org. Chem.* **2013**, 1749–1757; b) J. Rehak, L. Fisera, J. Kozisek, L. Bellovicova, *Tetrahedron* **2011**, *67*, 5762–5769; c) E. A. Brock, S. G. Davies, J. A. Lee, P. M. Roberts, J. E. Thomson, *Org. Lett.* **2011**, *13*, 1594–1597; d) X. Garrabou, L. Gomez, J. Joglar, S. Gil, T. Parella, J. Bujons, P. Clapes, *Chem. Eur. J.* **2010**, *16*, 10691–10706; e) I. Izquierdo, M.-T. Plaza, F. Franco, *Tetrahedron: Asymmetry* **2004**, *15*, 1465–1469; f) see ref.[13g]; g) O. Affolter, A. Baro, W. Frey, S. Laschat, *Tetrahedron* **2009**, *65*, 6626–6634; h) I. Izquierdo, M.-T. Plaza, R. Robles, F. Franco, *Tetrahedron: Asymmetry* **2001**, *12*, 2481–2487; i) H. Yoda, F. Asai, K. Takabe, *Synlett* **2000**, 1001–1003.
[15] a) H. Tokuyama, S. Yokoshima, S.-C. Lin, L. Li, T. Fukuyama, *Synthesis* **2002**, 1121–1123; b) M. Trajkovic, Z. Ferjancic, R. N. Saicic, *Org. Biomol. Chem.* **2011**, *9*, 6927–6929.
[16] A similar conformational phenomenon was earlier observed in the case of γ-mercaptoaldols, which spontaneously cyclized into hemithioacetals: J. Fanton, F. Camps, J. A. Castillo, C. Guerard-Helaine, M. Lemaire, F. Charmanttray, L. Hecquet, *Eur. J. Org. Chem.* **2012**, 203–210.
[17] The melting point of **6** was also determined with a WRS-1B Digital melting-point apparatus and it was found to be 166 °C, uncorrected.
[18] Note that the enantiomer was synthetized; therefore, the sign of the optical rotation is opposite.
[19] While this work was in progress, a similar approach to hyacinthacine analogues by using prolinal as the aldehyde acceptor was disclosed: K. A. Delawarally, *M.S. Thesis*, University of Saskatchewan, Saskatoon, Canada, **2011**; whereas in the matched case the result was comparable, the mismatched combination was not synthetically useful. Apparently, this supports our presumption that acyclic aldehydes would be a better choice as reaction partners.

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