JOC*Note*

Diastereoselective Preparation of Substituted δ-Valerolactones. Synthesis of (3*R*,4*S*)- and (3*R*,4*R*)-Simplactones

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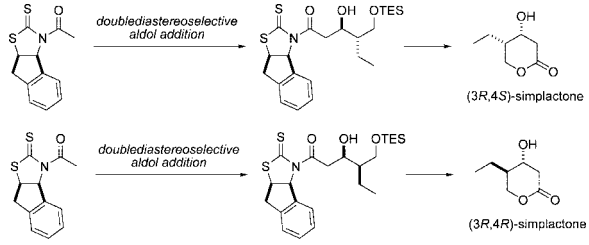
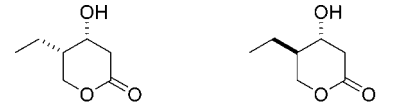


The syntheses of simplactones (3*R*,4*S*)-**1** and (3*R*,4*R*)-**2** were achieved in 5 steps from *N*-acyl thiazolidinethione chiral auxiliaries. The syntheses feature a double diastereoselective acetate aldol reaction solely controlled by the chirality of the auxiliary. Highly diastereoselective aldol reactions with *s*-trioxane were also achieved with *N*-acyl thiazolidinethione auxiliaries and the stereochemistry of an aldol product confirmed by X-ray analysis.

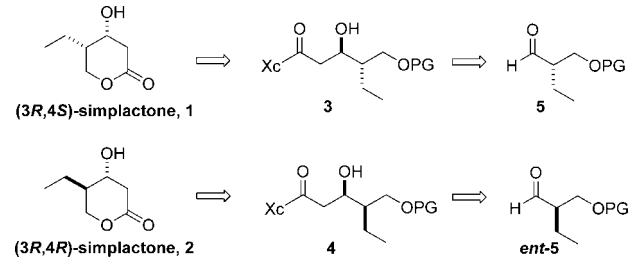
Recent advances in the acetate aldol reaction with chiral auxiliaries have resulted in practical and efficient methods to prepare α-unsubtituted aldol products with excellent diastereoselectivities.[1,2] Recently, we reported a conformationally rigid indene-based thiazolidinethione chiral auxiliary and demonstrated its utility in propionate and acetate aldol reactions with a variety of simple aldehydes and in a formal synthesis of aurisides.[3,4] Sammakia[5] and Crimmins[6] have shown that more sterically encumbered thiazolidinethione chiral auxiliaries deliver aldol products with excellent stereocontrol when added to chiral aldehydes. Titanium enolates derived from thiazolidinethiones and oxazolidinethiones added to different types of chiral aldehyde delivered products under the control of the chiral auxiliary over-riding the facial control of the stereochemistry of the aldehydes. The predictable stereoselectivity of products in these double diastereoselective aldol reactions should increase their use in the synthesis of natural products.[7] In this Note, we describe the acetate aldol reaction with enantiopure aldehydes in the preparation of natural products simplactones A and B, and other substituted δ-valerolactones that can find value for the synthesis of polyketide natural products possessing a hemiketal tetrahydropyran ring.[8]



(3*R*,4*S*)-simplactone, 1 (3*R*,4*R*)-simplactone, 2

Simplactones A and B were isolated in minute amount from the Caribbean sponge *Plakortis simplex* by Fattorusso's group in 1999.[9] One of these simplactones exhibited moderate cytotoxicity against WEHI-164, murine fibrosarcoma cells. Ogasawara prepared the (3*R*,4*R*)- and the (3*R*,4*S*)-simplactones from enantiopure 4-cumyloxy-2-cyclopenten-1-one and revised the structures initially reported.[10] Ogasawara found that the (3*R*,4*R*)-simplactone's spectroscopic data (and sign, but not value, of the optical rotation) matched the one reported for simplactone A. The ^{1}H but not the ^{13}C NMR data of simplactone (3*R*,4*S*) matched that of simplactone B. To avoid any confusion, we refer to these lactones using their absolute configuration. A second synthesis of (3*R*,4*R*)-simplactone was accomplished in six steps featuring a boron enolate aldol reaction to create the two stereogenic centers.[11] The same simplactone was also synthesized starting from (*R*)-glycidyl ether in nine steps and featuring a Prins reaction.[12]

SCHEME 1. Retrosynthetic Analyses of Simplactones



Because of our interest in studying acetate aldol reactions with nonracemic aldehydes using the new Indane-based thiazolidinethione, we envisioned syntheses of simplactones using the double diastereoselective aldol products **3** and **4**, Scheme 1. Acetate aldol reactions to chiral aldehydes **5** and *ent*-**5** should

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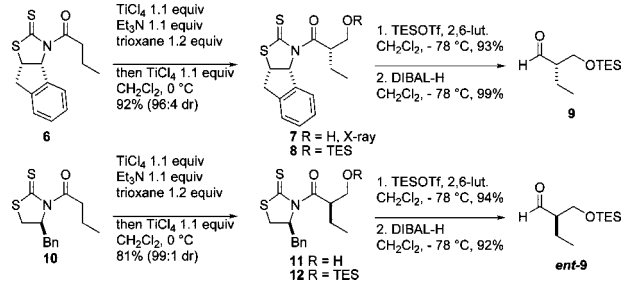
SCHEME 2. Preparation of Enantiopure Aldehydes 9 and *ent*-9



give the desired aldol products when the chiral auxiliary is a thiazolidinethione that directs the stereochemistry of the prochiral center.

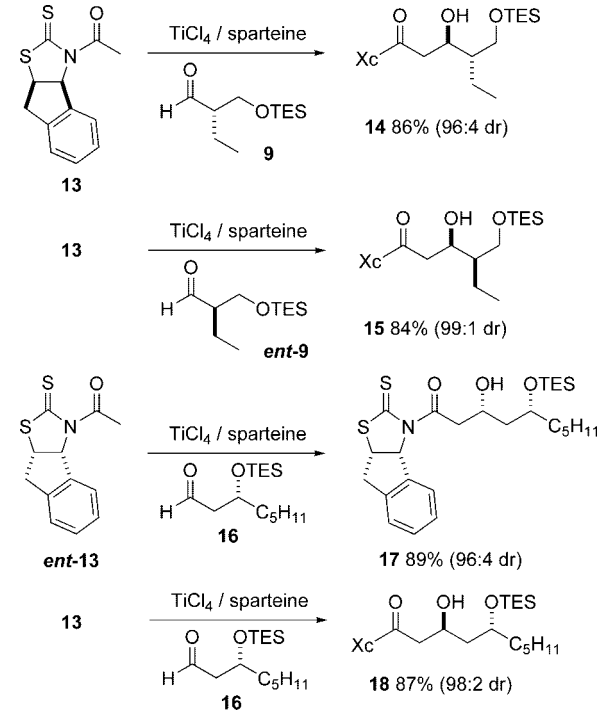
We prepared the two enantiomeric aldehydes **9** and *ent*-**9** via aldol reaction using a thiazolidinethione auxiliary derived from phenylalanine and an indene-based thiazolidinethione prepared from (1*R*,2*R*)-amino-2-indanol, Scheme 2. The corresponding *N*-butanoyl thiazolidinethiones **6** and **10** were prepared by addition of the acid chloride to the corresponding thiazolidinethione with triethylamine and dichloromethane at 0 °C in high yields. Aldol reaction of *N*-acyl thiazolidinethiones with trioxane was carried out following Evans protocol for similar reactions with oxazolidinone chiral auxiliaries.[13] The aldol reaction with trioxane delivered the aldol products in very good yields and high diastereoselectivities. An X-ray crystallographic analysis of aldol product **7** confirmed its stereochemistry unambiguously. Protection of the aldol products **7** and **11** as their silyl ethers and partial reduction with dibal-H afforded the corresponding aldehydes **9** and *ent*-**9** in excellent yields.

Acetate aldol reactions with enantiopure aldehydes were carried out with Crimmins optimized conditions, Scheme 3.[14] A solution of Ti(IV) chloride (1 equiv) and (−)-sparteine (1 equiv) was added to the *N*-acetyl thiazolidinethione **13** to form the metal enolate. Aldehyde (0.9 equiv) was added to the reaction mixture at − 78 °C. *N*-Acetyl thiazolidinethione **13** was reacted with aldehyde **9** and also with its enantiomer delivering aldol products **14** and **15**, respectively, in high yields and diastereoselectivities. Similarly, enantipure aldehyde **16**, prepared in three steps via acetate aldol reaction, was reacted with *N*-acetyl thiazolidinethione **13** and also with its antipode *ent*-**13** delivering aldol products **17** and **18** in very good yields and excellent diastereoselectivities. Aldol products **14** and **15** were utilized for the syntheses of simplactones, which proved their stereochemistry. We observed that only the chirality of the chiral auxiliary played a role in the stereochemical outcome of the aldol products with enantipure aldehydes.

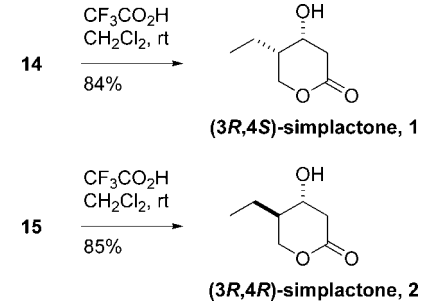
Treatment of aldol products **14** and **15** with trifluoroacetic acid in dichloromethane at room temperature removed the silyl protecting groups and sparked cyclization to furnish the corresponding simplactones (3*R*,4*S*) and (3*R*,4*R*), respectively, in good yields, Scheme 4. Both the spectroscopic data of simplactones and their optical rotation were in agreement with those reported by Ogasawara.[10] The syntheses of these two simplactones confirmed the stereochemistry of the aldol products.

The other two aldol products **17** and **18** were transformed into their acetonides **19** and **20**, respectively, to confirm their relative stereochemistry, using Rychnovsky's method, Scheme 5.[15] Indeed, the 1,3-*syn* acetonide's methyl groups showed ^{13}C NMR peaks with very different chemical shifts, while the 1,3-*anti* acetonide's methyl group chemical shift peaks were very similar.

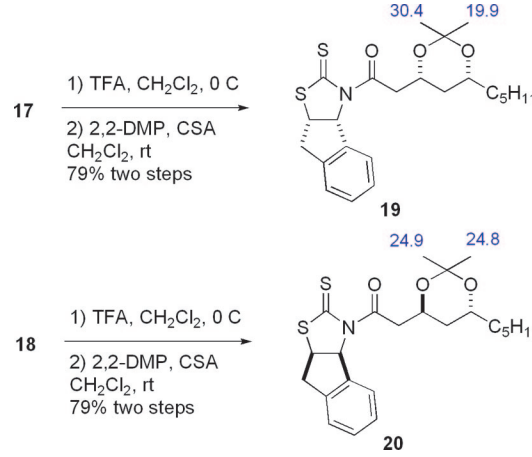
SCHEME 3. Double Diastereoselective Acetate Aldol Reactions



SCHEME 4. Tandem Deprotection and Cyclization



SCHEME 5. Preparation of Acetonides



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In summary, we have shown that the stereochemical outcome of the acetate aldol reactions mediated by the indene-based thiazolidienthione chiral auxiliary is driven solely by the chirality of the auxiliary and not by the chirality of the chiral aldehyde. The double diastereoselective acetate aldol reactions were valuable for very short syntheses of both (3*R*,4*S*)- and (3*R*,4*R*)-simplactones.

Experimental Section

General Procedure for Acetate Aldol Reaction with Chiral Aldehydes. To a stirred yellow solution of *N*-acetate thiazolidinethione **13** (498 mg, 2 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added a solution of $TiCl_4$ (2 mL, 2 mmol, 1 M CH_2Cl_2 soln.) dropwise over 5 min under argon atmosphere. The yellow slurry was stirred at −78 °C for 10 min. A solution of (−)-sparteine (469 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 5 min to the reaction mixture. The deep-red reaction mixture was stirred at −78 °C for 30 min. A solution of aldehyde **9** (389 mg, 1.8 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise over 10 min to the reaction mixture. The reaction mixture was stirred at −78 °C for 2.5 h. The reaction was quenched by addition of $NaHCO_3$ sat. soln. (0.5 mL) at −78 °C and stirred while reaching room temperature for 5 min. More $NaHCO_3$ sat. soln. (10 mL) was added. The organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give a yellow thick oil. ^{1}H NMR analysis on the crude reaction indicated 96:4 dr (δ_H 4.41 major diastereomer and δ_H 4.51 minor diastereomer). The residue was purified by flash column chromatography on a (3 cm × 14 cm) silica gel column (petroleum ether−ethyl acetate, 75:25) to give the aldol product **14** as yellow foam: 719 mg, 86% yield.

***syn*-Acetate Aldol 14.** Yellow foam; R_f 0.38 (75:25, petroleum ether−ethyl acetate); $[\alpha]^{22}_D$ +433.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.43 (1H, m), 7.37−7.27 (3H, m), 6.61 (1H, d, J = 7.0 Hz), 4.57 (1H, dd, J = 7.0, 6.1 Hz), 4.42 (1H, dddd, J = 9.1, 8.8, 5.7, 3.2 Hz), 3.93 (1H, dd, J = 10.2, 3.3 Hz), 3.76 (1H, d, J = 5.7 Hz), 3.74 (1H, dd, J = 10.2, 4.8 Hz), 3.62 (1H, dd, J = 17.0, 9.1 Hz), 3.52 (1H, dd, J = 17.0, 3.2 Hz), 3.39 (1H, dd, J = 17.0, 6.1 Hz), 3.14 (1H, d, J = 17.0 Hz), 1.65−1.40 (3H, m), 0.98 (3H, t, J = 7.4 Hz), 0.97 (9H, t, J = 7.7 Hz), 0.62 (6H, q, J = 7.7 Hz). ^{13}C NMR ($CDCl_3$) δ 201.5 (CS), 173.9 (CO), 139.2 (C), 139.0 (C), 129.6 (CH), 128.3 (CH), 126.2 (CH), 125.3 (CH), 75.9 (CH), 70.8 (CH), 63.9 (CH_2), 47.4 (CH), 46.1 (CH), 44.6 (CH_2), 36.3 (CH_2), 21.3 (CH_2), 12.0 (CH_3), 6.9 ($3CH_3$), 4.4 ($3CH_2$). HRMS (EI) calcd for ($C_{23}H_{35}NO_3S_2Si$) *m*/*z* 465.1828, found *m*/*z* 465.1833.

***syn*-Acetate Aldol Product 15.** Yellow oil; R_f 0.33 (75:25, petroleum ether−ethyl acetate); $[\alpha]^{22}_D$ +401.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.43 (1H, m), 7.38−7.28 (3H, m), 6.61 (1H, d, J = 7.0 Hz), 4.58 (1H, dd, J = 7.0, 6.0 Hz), 4.52 (1H, ddd, J = 10.0, 3.8, 2.5 Hz), 3.82 (1H, dd, J = 10.3, 4.1 Hz), 3.75 (1H, dd, J = 10.3, 6.8 Hz), 3.69 (1H, d, J = 4.9 Hz), 3.61 (1H, dd, J = 17.2, 10.0 Hz), 3.40 (1H, dd, J = 17.0, 6.0 Hz), 3.38 (1H, dd, J = 17.2, 3.8 Hz), 3.14 (1H, d, J = 17.0 Hz), 1.70 (1H, m), 1.46−1.38 (2H, m), 0.97 (9H, t, J = 8.0 Hz), 0.97 (3H, t, overlapped), 0.62 (6H, q, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ 201.5 (CS), 174.0 (CO), 139.2 (C), 139.1 (C), 129.6 (CH), 128.3 (CH), 126.2 (CH), 125.3 (CH), 75.9 (CH), 70.9 (CH), 64.4 (CH_2), 47.4 (CH), 46.4 (CH), 42.9 (CH_2), 36.4 (CH_2), 19.2 (CH_2), 12.5 (CH_3), 6.9 ($3CH_3$), 4.4 ($3CH_2$). HRMS (ESI) calcd for ($C_{23}H_{35}NO_3S_2Si$) *m*/*z* 465.1828, found *m*/*z* 465.1837.

***syn*-Acetate Aldol Product 17.** Yellow solid; mp 99−100 °C; R_f 0.36 (6:4, petroleum ether−ethyl acetate); $[\alpha]^{22}_D$ −428.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.42−7.27 (4H, m), 6.61 (1H, d, J = 7.0 Hz), 4.57 (1H, dd, J = 7.0, 6.1 Hz), 4.43 (1H, m), 3.99 (1H, dd, m), 3.62 (1H, d, J = 2.1 Hz), 3.59 (1H, dd, J = 17.5, 3.1 Hz), 3.39 (1H, dd, J = 17.0, 6.1 Hz), 3.34 (1H, dd, J = 17.5, 8.8 Hz), 3.14 (1H, d, J = 17.0 Hz), 1.74−1.70 (2H, m), 1.56−1.49 (2H, m), 1.35−1.27 (6H, m), 0.97 (9H, t, J = 8.1 Hz), 0.90 (3H, t, J = 7.1 Hz), 0.64 (6H, q, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 201.4 (CS), 173.5 (CO), 139.1 (C), 138.9 (C), 129.6 (CH), 128.3 (CH), 126.1 (CH), 125.3 (CH), 75.7 (CH), 72.4 (CH), 67.3 (CH), 47.3 (CH), 46.3 (CH_2), 42.7 (CH_2), 37.9 (CH_2), 36.4 (CH_2), 32.2 (CH_2), 24.8 (CH_2), 14.2 (CH_3), 7.1 ($3CH_3$), 5.3 ($3CH_2$).

***syn*-Acetate Aldol Product 18.** Yellow oil; R_f 0.30 (75:25, petroleum ether−ethyl acetate); $[\alpha]^{22}_D$ +385.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.41−7.28 (4H, m), 6.60 (1H, d, J = 7.0 Hz), 4.57 (1H, dd, J = 7.0, 6.1 Hz), 4.32 (1H, m), 3.98 (1H, m), 3.73 (1H, d, J = 2.6 Hz), 3.58 (1H, dd, J = 17.1, 7.5 Hz), 3.49 (1H, dd, J = 17.1, 4.7 Hz), 3.40 (1H, dd, J = 17.0, 6.1 Hz), 3.15 (1H, d, J = 17.0 Hz), 1.75−1.70 (2H, m), 1.55−1.47 (2H, m), 1.37−1.25 (6H, m), 0.98 (9H, t, J = 8.0 Hz), 0.89 (3H, t, J = 7.1 Hz), 0.64 (6H, q, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 201.4 (CS), 174.0 (CO), 139.1 (C), 138.8 (C), 129.7 (CH), 128.4 (CH), 126.1 (CH), 125.3 (CH), 75.7 (CH), 71.9 (CH), 67.5 (CH), 47.2 (CH), 45.9 (CH_2), 43.1 (CH_2), 37.7 (CH_2), 36.4 (CH_2), 32.2 (CH_2), 24.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3), 7.1 ($3CH_3$), 5.3 ($3CH_2$).

(3*R*,4*S*)-Simplactone 1. To a stirred yellow solution of acetate aldol product **14** (232 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) at room temperature was added TFA (3 drops). The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was washed with $NaHCO_3$ sat. soln. (5 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to give a white solid. The residue was purified by flash column chromatography on a (2 cm × 12 cm) silica gel column (petroleum ether−ethyl acetate, 3:7) to give simplactone as a colorless oil: 60 mg, 84% yield; R_f 0.28 (3:7, petroleum ether−ethyl acetate); $[\alpha]^{22}_D$ +23.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.36 (1H, dd, J = 11.1, 10.8 Hz), 4.24 (1H, dd, J = 11.1, 5.4 Hz), 4.20 (1H, bd, J = 2.8 Hz), 2.80 (1H, bs), 2.74 (1H, dd, J = 18.2, 3.1 Hz), 2.65 (1H, dd, J = 18.2, 3.9 Hz), 1.84 (1H, m), 1.47 (1H, ddq, J = 13.7, 7.4, 2.3 Hz), 1.35 (1H, ddq, J = 13.7, 7.4, 2.8 Hz), 0.98 (3H, t, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 170.9 (CO), 69.2 (CH_2), 64.5 (CH), 39.4 (CH), 39.3 (CH_2), 19.7 (CH_2), 11.4 (CH_3).

(3*R*,4*R*)-Simplactone 2. To a stirred yellow solution of acetate aldol product **15** (70 mg, 0.15 mmol) in CH_2Cl_2 (15 mL) at room temperature was added trifluoroacetic acid (2 drops). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was treated with $NaHCO_3$ sat. soln. (5 mL) and stirred at room temperature for 5 min. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to give a light yellow oil. The residue was purified by flash column chromatography on a (2 cm × 10 cm) silica gel column (petroleum ether−ethyl acetate, 3:7) to give simplactone as a colorless oil: 17.9 mg, 85% yield. R_f 0.34 (3:7, petroleum ether−ethyl acetate); $[\alpha]^{22}_D$ −25.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.49 (1H, dd, J = 11.5, 4.5 Hz), 3.97 (1H, dd, J = 11.5, 7.8 Hz), 3.96 (1H, overlapped), 2.86 (1H, dd, J = 17.4, 5.6 Hz), 2.61 (1H, bs), 2.55 (1H, dd, J = 17.4, 5.8 Hz), 1.78 (1H, m), 1.63 (1H, ddq, J = 14.0, 7.4, 5.4 Hz), 1.35 (1H, ddq, J = 14.0, 8.5, 7.4 Hz), 1.01 (3H, t, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 171.0 (CO), 69.3 (CH_2), 68.1 (CH), 42.6 (CH), 38.3 (CH_2), 21.8 (CH_2), 11.4 (CH_3).

General Procedure for Preparation of Acetonides. Trifluoroacetic acid (0.2 mL) was added to a stirred yellow solution of aldol product **17** (111 mg, 0.22 mmol) in 5 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 90 min. The volatiles were evaporated and the residue was dissolved in CH_2Cl_2 (5 mL). 2,2-Dimethoxypropane (0.2 mL) and one crystal of camphor sulfonic acid were successively added over the solution. The reaction mixture was stirred overnight. The reaction mixture was treated with 5 mL of sat. $NaHCO_3$ soln. and stirred for 5 min. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash column chromatography on a (2 cm × 10 cm) silica gel column (petroleum

ether−ethyl acetate, 8:2) to give the title acetonide as a yellow solid: 75 mg, 79% yield.

***syn*-Acetonide 19.** R_f 0.33 (8:2, petroleum ether−ethyl acetate); $[\alpha]^{22}_D$ −414.2 (*c* 1.0, $CHCl_3$). Mp 56−57 °C. ^{1}H NMR ($CDCl_3$) δ 7.41−7.37 (4H, m), 6.57 (1H, d, J = 7.0 Hz), 4.60−4.52 (2H, m), 3.86 (1H, m), 3.50 (1H, dd, J = 17.2, 3.8 Hz), 3.41 (1H, dd, J = 17.0, 6.0 Hz), 3.40 (1H, dd, J = 17.2, 7.7 Hz), 3.15 (1H, d, J = 17.0 Hz), 1.64 (1H, m), 1.43−1.36 (2H, m), 1.47 (3H, s), 1.39 (3H, s), 1.33−1.25 (6H, m), 0.89 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 201.3 (CS), 172.2 (CO), 139.2 (C), 138.9 (C), 129.6 (CH), 128.3 (CH), 126.2 (CH), 125.3 (CH), 98.9 (C), 75.9 (CH), 69.2 (CH), 65.9 (CH), 47.3 (CH), 45.4 (CH_2), 36.7 (CH_2), 36.5 (CH_2), 36.4 (CH_2), 31.9 (CH_2), 30.4 (CH_3), 24.8 (CH_2), 22.8 (CH_2), 19.9 (CH_3), 14.2 (CH_3).

***anti*-Acetonide 20.** Yellow oil; R_f 0.35 (8:2, petroleum ether−ethyl acetate); $[\alpha]^{22}_D$ +419.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.41−7.27 (4H, m), 6.55 (1H, d, J = 7.1 Hz), 4.57 (1H, dd, J = 7.1, 6.1 Hz), 4.52 (1H, m), 3.80 (1H, m), 3.50 (1H, dd, J = 17.5, 7.7 Hz), 3.44 (1H, dd, J = 17.5, 4.6 Hz), 3.39 (1H, dd, J = 17.0, 6.1 Hz), 3.14 (1H, d, J = 17.0 Hz), 1.76−1.71 (2H, m), 1.56−1.43 (2H, m), 1.40 (3H, s), 1.35 (3H, s), 1.32−1.25 (6H, m), 0.89 (3H, t, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 201.4 (CS), 172.1 (CO), 139.2 (C), 138.9 (C), 129.6 (CH), 128.3 (CH), 126.2 (CH), 125.3 (CH), 100.8 (C), 75.9 (CH), 66.8 (CH), 63.3 (CH), 47.4 (CH), 44.7 (CH_2), 38.3 (CH_2), 36.4 (CH_2), 36.0 (CH_2), 31.9 (CH_2), 25.2 (CH2), 24.9 (CH_3), 24.8 (CH_3), 22.8 (CH_2), 14.3 (CH_3).

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Supporting Information Available: Copies of ^{1}H and ^{13}C spectra for compounds **1**, **2**, **6**−**20**, an ortep drawing and CIF file for the X-ray structure of aldol product **7**, and expermental details for compounds **6**−**9**, **11**, **12**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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