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Diastereoselectivities Realized in the Amino Acid Catalyzed Aldol Cyclizations of Triketo Acetonides of Differing Ring Size

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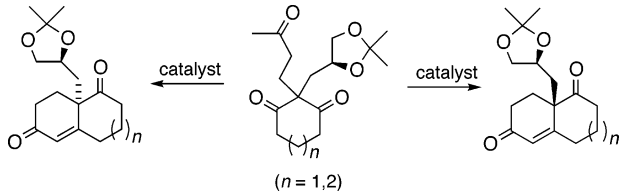
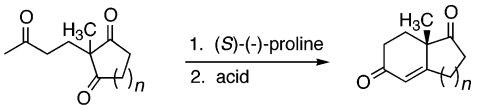


A study designed to assess the diastereoselectivity of the intramolecular aldol reaction of two differently sized monocyclic 1,3-diketones bearing a chiral, oxygenated side chain has been undertaken. The cyclizations were brought about under catalysis by pyrrolidine, a series of D- and L-amino acids including proline, and several proline derivatives. The levels of selectivity were found to be consistently higher with the six-membered ring system than its cycloheptane counterpart.

In the mid-to-early 1970s, the capability of L-(−)-proline to promote the intramolecular aldolization of prochiral triketones **1** in a highly enantioselective manner gained considerable recognition.[1,2] Progression from these discoveries saw the Hajos−Parrish ketone (**2a**)[3] and the Wieland−Miescher homologue **2b**[4] adopted as enantioenriched starting materials for numerous targeted syntheses. Beyond this, catalysis of the Robinson annulation by D-(+)-proline has been implemented as warranted.[5] Also to come under intense scrutiny were the mechanistic details of this asymmetric transformation. Presently, enamine intermediates are recognized to be involved,[6] with C−C bond formation serving as the rate-determining step.[7]



1a, *n* = 1
b, *n* = 2

2a, *n* = 1
b, *n* = 2

Bicyclic ketones related to **2b** but carrying an oxygenated angular methyl group have been elaborated by means of related protocols. These include the ester **3**[8] as well as the masked hydroxymethyl derivatives **4a**−**c**.[9−11]

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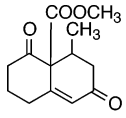

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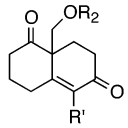
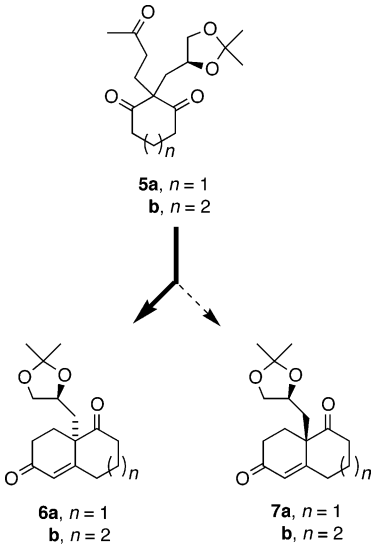


4a, R' = H; R^2 = MEM
b, R' = CH_3; R^2 = MOM
c, R' = H; R^2 = MOM

In connection with an ongoing synthetic project, we had need to prepare quantities of the enantiomerically pure diketo acetonides **6a** and **6b**. The presence of a stereodefined stereogenic center in **5** allowed for examination of the contribution of this quite remote site on product diastereoselection as defined by the ratio of **6/7**. Our

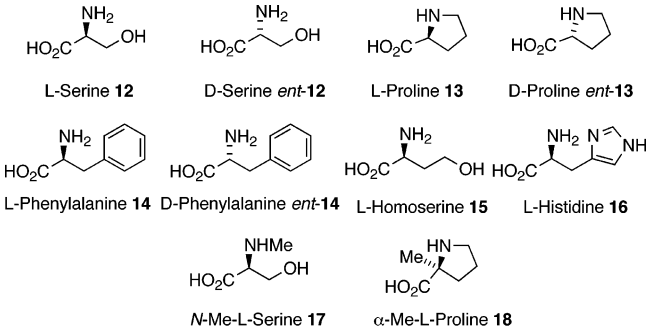


5a, *n* = 1
b, *n* = 2

6a, *n* = 1
b, *n* = 2

7a, *n* = 1
b, *n* = 2

expectation was that contributions from the acetonide moiety to partitioning between the two competing cyclization events would be low. On the other hand, catalysis studies involving amino acids of varying type (Figure 1) and substituted proline derivatives (Figure 2)[12,13] were expected to shed light on the potential for diastereocontrol of the ring formation. Pyrrolidine-like secondary amines such as **20**−**23** are recognized to be capable of acting as serviceable catalysts in asymmetric aldol reactions.[14,15] The recent example of efficient enan-

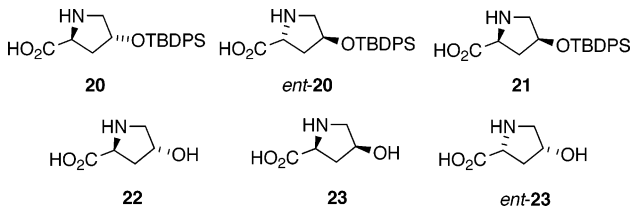


L-Serine **12** D-Serine *ent*-**12** L-Proline **13** D-Proline *ent*-**13**

L-Phenylalanine **14** D-Phenylalanine *ent*-**14** L-Homoserine **15** L-Histidine **16**

N-Me-L-Serine **17** α-Me-L-Proline **18**

FIGURE 1. Amino acids screened as catalysts.

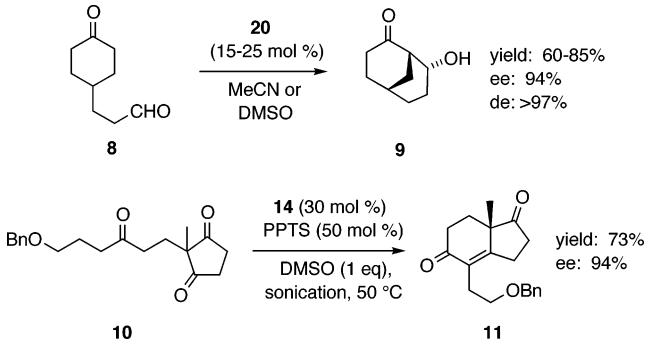


20 *ent*-**20** **21**

22 **23** *ent*-**23**

FIGURE 2. Proline derivatives involved in this study.

SCHEME 1



tioselective cyclization of **8** as promoted by the L-proline derivative **20** has been reported by Iwabuchi[16] (Scheme 1). The remarkable effect of *p*-toluenesulfonic acid as a co-additive for production of the α-substituted Wieland−Miescher ketone **11** also prompted us to explore Shibasaki's conditions.[17]

Results and Discussion

Knoevenagel-type condensation of commercially available **24a** or 1,3-cycloheptanedione (**24b**)[18] with enantiopure D-glyceraldehyde acetonide[19] in the presence of silica gel and an excess of thiophenol in dichloromethane or benzene furnished diketones **25a** and **25b**, respectively, in good yield (Scheme 2). The thiophenol was necessary to thwart 2-fold addition of the 1,3-diketones to aldehyde **19**.[20] NMR data showed evidence of good

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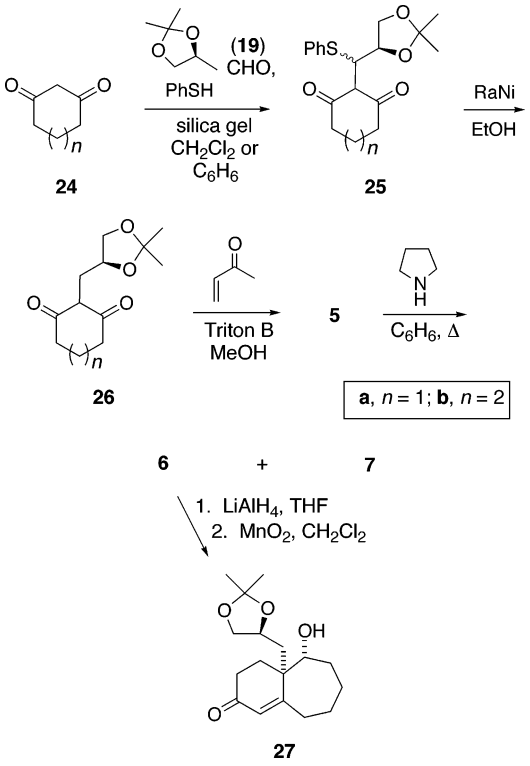
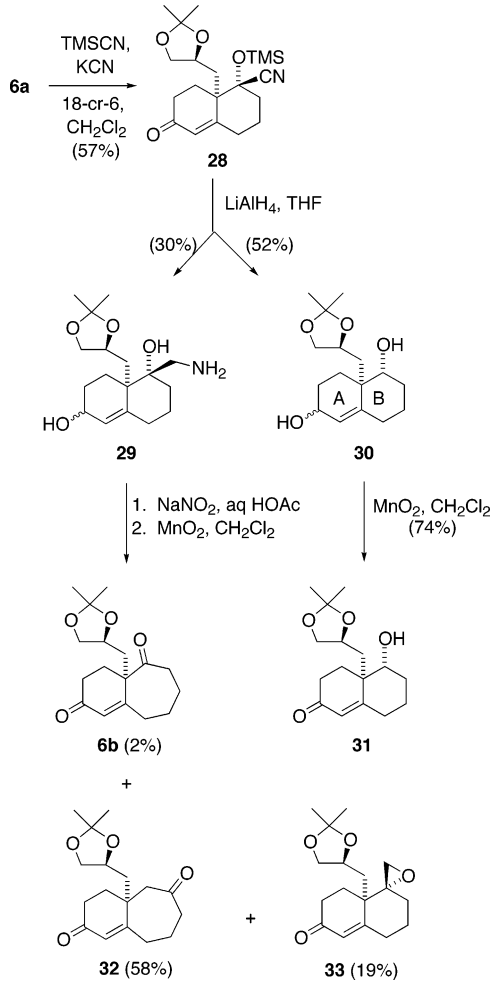
SCHEME 2



SCHEME 3



diastereoselectivity in this step, but this issue was not investigated further. Following the desulfurization of diketones **25** with Raney nickel, formation of the quaternary center was realized by 1,4-addition to methyl vinyl ketone in the presence of Triton B.[21] The pyrrolidine-mediated intramolecular cyclization of **26a** and **26b** afforded diastereomeric mixtures of **6** and **7**, the composition of which was ascertained by integration of high-field ^{1}H NMR spectra recorded on $CDCl_3$ solutions of unpurified products. The relevant signals of the olefinic protons appear at the following chemical shifts: **6a**, δ 5.90; **6b**, δ 6.06; **7a**, δ 5.88; **7b**, δ 6.16.

Both diastereomeric pairs proved to be readily separated by chromatography on silica gel. The controlled lithium aluminum hydride reduction of **6b** gave rise to the highly crystalline keto alcohol **27**, thus allowing for unequivocal assignment of absolute configuration by means of X-ray crystallography. The **a** and **b** series were intercorrelated by chemical means involving expansion of the saturated ring in **6a**. This ketone lent itself conveniently to the regioselective and stereoselective addition of trimethylsilyl cyanide[22] in the presence of KCN and 18-crown-6[23] (Scheme 3). When **28** was subsequently reduced with lithium aluminum hydride in THF, the amino diol **29** was formed (30%) alongside diol **30** (52%). The latter product was obviously generated by retrogession back to **6a** under the reaction conditions followed by in situ reduction at two sites. An investigation of conditions that would give rise to heightened levels of **29** was not undertaken. However, the oxidation of **30** with manganese dioxide to furnish exclusively **31** established that its diastereomeric composition was due to nonstereoselective hydride transfer to ring A and not to ring B.

Diazotization of **29** with sodium nitrite in aqueous acetic acid[24] resulted in the generation of a number of products. Direct oxidation of the allylic alcohol functionality simplified matters to the three-component level. Following chromatographic separation, it became clear that 1,2-migration of the quaternary carbon is the dominant reaction pathway (58% of **32**) after generation of the diazonium ion.[25] Epoxide generation as in **33** (19%) is somewhat less prevalent. Despite the low percent conversion to **6b**, adequate amounts were made available to link **6a** structurally to **6b**, thereby confirming all stereochemical assignments.

The results obtained during the pyrrolidine-induced aldol cyclizations of **5a** and **5b** in methanol provided the first indication that this pair of homologues might well exhibit distinguishably different chemical responses. Thus, **5a** was transformed under these conditions into a complex product mixture (entry 1, Table 1). In the second

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TABLE 1. Asymmetric Aldol Reactions of 5a Involving Catalysis by Proline Derivative

entry	catalyst (equiv)	solvent/ *T* (°C)	time, h	yield,[a] %	ratio **6a/7a**[b]	de,[c] %
1	pyrrolidine (1:1)	MeOH/rt	16	complex mixture		
2	**13** (0.1)	DMSO/rt	48	34	7:93	−86
3	**13** (0.2)	DMSO/50 °C	21	52[d]	8:92	−84
4	**13** (0.2)	MeCN/rt	48	8[d]	10:90	−80
5	**20** (0.2)	DMSO/rt	48	51	10:90	−80
6	**20** (0.2)	DMSO/50 °C	16	**76**	**10:90**	**−80**
7	**20** (0.2)	MeCN/rt	48	55[d]	8:92	−84
8	**20** (0.2)	DMF/rt	48	66[d]	23:77	−54
9	*ent*-**20** (0.2)	DMSO/rt	48	40	76:24	52
10	*ent*-**20** (0.2)	DMSO/50 °C	23	61	80:20	60

[a] Isolated yield. [b] The **6a/7a** ratios were determined from the ^{1}H NMR spectra at 300 MHz of the crude products by integration of the signals due to the olefinic process. [c] Opposite diastereoselection is assigned as minus. [d] Percent conversion.

TABLE 2. Diastereoselective Aldol Reactions of 5b Involving Catalysis by Pyrrolidine and Select Amino Acids

entry	amino acids	solvent	time, h	yield,[a] %	ratio **6b/7b**[b]	de,[c] %
11	pyrrolidine	benzene	2.5	60	43:57	−14
12	pyrrolidine	MeOH	0.5	56	41:59	−18
13	**12**	MeOH	9.0	**79**	**38:62**	**−24**
14	*ent*-**12**	MeOH	7.5	75	39:61	−22
15	*ent*-**12**	DMSO	10	34	39:61	−22
16	**13**	MeOH	1.5	77	47:53	−6
17	*ent*-**13**	DMF	3.0	51	45:55	−10
18	**14**	MeOH	8.5	66	43:57	−14
19	*ent*-**14**	DMSO	10	28	31:69	−38
20	**15**	MeOH	6.0	75	34:66	−32
21	**16**	MeOH	14.5	**88**	**35:65**	**−30**
22	**17**	MeOH	36	39[d]	27:63	−46
23	**18**	MeOH	36	3[d]	38:62	−24

[a] Isolated yield. [b] The **6b/7b** ratios were determined from the ^{1}H NMR spectra at 300 MHz of the crude products by integration of the signals due to the olefinic process. [c] Opposite diastereoselection is assigned as minus. [d] Percent conversion.

instance, ring closure occurred with modest efficiency to deliver a 41:59 mixture of **6b/7b** (entry 12, Table 2). The product distribution remains unaltered in benzene as solvent (entry 11, Table 2), thereby indicating that the acetonide subunit is not capable in its own right to engage in a reasonably useful level of stereochemical control. However, heightened levels of diastereomeric bias were noted when the aldol reaction of **5a** was promoted with L-proline (**13**). Recourse to this catalyst resulted in the observation of **6a/7a** ratios of 10:90 in either DMSO or acetonitrile as reaction medium (entries 2−4). Annulation of the seven-membered ring as in the case of **6b/7b** was not comparably effective (∼45:55, entries 16 and 17). Recourse to other amino acids including D- and L-serine, D- and L-phenylalanine, L-homoserine, L-histidine, *N*-methyl-L-serine, and α-methyl-L-proline did not give evidence of comparable or superior diastereomeric ratios (Table 1).

As this study was extended to include the proline derivatives **20**−**23**, it was found that the maximum 10:90 diastereomeric ratio earlier observed for **5a** could be matched by **20** in DMSO at 50 °C, in tandem with a useful increase in yield to the 76% level (entry 6). By analogy, it was expected that **5b** would exhibit a similar enhancement in its diastereoselectivity profile. Disappointingly, the associated range of results proved not to be broadly observed. The data compiled in Table 3 hovered most often around 50:50, on occasion rising to 60:40 (entries 24−33). Close examination of the product mixtures involving the use of pyridinium *p*-toluenesulfonate as a co-catalyst did not provide any sign of improvement.

TABLE 3. Diastereoselective Aldol Reactions of 5b Involving Catalysis by Pyrrolidine and Select Amino Acids

entry	proline	additive (equiv)	solvent	time, h	yield,[a] %	ratio **6b/7b**[b]	de,[c] %
24	**20** (1.1)		MeOH	2.5	75	58:42	16
25	*ent*-**20** (1.1)		MeOH	1.5	71	39:62	−22
26	**21** (1.1)		MeOH	1.5	64	50:50	0
27	**22** (1.1)		MeOH	3.0	79	53:47	6
28	**23** (1.1)		MeOH	2.5	66	47:53	−6
29	*ent*-**23** (1.1)		MeOH	4.0	83	37:63	−26
30	**20** (1.1)		MeCN	9.5	30	59:41	18
31	**20** (1.1)		DMF	5.5	60	51:49	2
32	**20** (1.1)		DMSO	1.0	62	50:50	0
33	**20** (1.1)		*i*-PrOH	1.0		47:53	−6
34	**20** (1.1)	PPTS (0.50)	DMSO	5.0	53[d]	50:50	0
35	**20** (1.1)	PPTS (0.50)	MeOH	4.0	17[d]	50:50	0
36	**20** (0.2)		MeOH	7.0	71	52:48	4

[a] Isolated yield. [b] The **6b/7b** ratios were determined from the ^{1}H NMR spectra at 300 MHz of the crude products by integration of the signals due to the olefinic process. [c] Opposite diastereoselection is assigned as minus. [d] Percent conversion.

In no cyclization involving **5b** could the proportion of **7b** be pushed above the 66% mark. For **5a**, the aldol product **7a** was often present at a level of 90% or above. This comparative analysis argues in favor of advancing to **6b** by the highly diastereoselective cyclization of **5a**. If this route is selected, then an improved means for regiodirected ring expansion requires development. Alternatively, the choice of beginning a campaign to arrive at **6b** from **5b** clearly would be facilitated by the discovery of a superior asymmetric catalyst system suited to improved transformation into this bicyclic enedione.

Although the proposed mechanism of the title reaction has enthusiastic supporters,[6,26−28] it is not at all apparent that a direct kinetic link between diastereoselectivity and ring size can be formulated. In the present examples as in their simpler structural counterparts, the use of *S*-proline directs reaction toward the *Si* face of the prochiral carbonyl. Beyond that, while the involvement of enamines is well supported, the exact nature of the ensuing chemical events has proven to be more elusive. Is the inability of a seven-membered ring to adopt a chair conformation akin to cyclohexyl systems responsible? Why is the small increase in energy associated with this

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phenomenon so disruptive of the preferred operation of one dominant pathway? A different option is that the charge stabilization associated with hydrogen bonding of the carboxylic acid proton to the developing alkoxide center is less easily attained for minor structural reasons. This feature of intermolecular aldol reactions and the geometry of the ensuing proton transfer could act in unison to impede the attainment of high quality stereoselectivity control.

Experimental Section

Compound 25a. To a stirred suspension of 1,3-cyclohexanedione (12.9 g, 0.12 mol), thiophenol (118 mL, 1.15 mol), and silica gel (19.35 g) in CH_2Cl_2 (400 mL) was added D-glyceraldehyde acetonide (22.5 g, 0.17 mol) at rt over 5 min. After being stirred for 48 h at the same temperature, the mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate) to afford a diastereomeric mixture (ca. 9:1) of **25a** (27.22 g, 68%) as a white solid. The major isomer was purified by recrystallization from ethyl acetate/hexanes to supply spectra. The mixture was used in the next reaction without further purification. For the pure major isomer of **25a**: colorless needles; mp 123−123.5 °C; IR (film, cm^{-1}) 1603; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.20 (m, 5H), 5.13 (d, J = 2.6 Hz, 1H), 4.53 (dt, J = 2.7, 7.5 Hz, 1H), 3.99 (dd, J = 6.7, 8.4 Hz, 1H), 3.40 (t, J = 8.4 Hz, 1H), 2.52−2.10 (m, 4H), 1.92−1.78 (m, 1H), 1.69−1.51 (m, 1H), 1.45 (s, 3H), 1.46−1.38 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 176.2, 133.2, 132.9, 128.72, 128.68, 127.6, 110.2, 110.0, 77.3, 66.9, 42.5, 36.0, 29.8, 25.4, 24.6, 20.1; ES HRMS m/z ($C_{18}H_{22}O_4SNa^+$) calcd 357.1131, obsd 357.1125; $[\alpha]^{21}_D$ +88.7 (c 1.52, benzene).

Compound 5a. To a stirred solution of **25a** (27 g, 80.8 mmol) in ethanol (300 mL) was added Raney nickel (67.5 mL, wet volume; 2.5 mL/1 g of substrate) suspended in ethanol (50 mL) at 0 °C over 10 min. After further stirring for 2 h at rt, the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate) to afford **26a** (15.7 g) as a colorless oil containing trace impurities. Without further purification, a solution of **26a** (15.7 g), methyl vinyl ketone (14.5 mL, 0.17 mol), and benzyltrimethylammonium hydroxide (Triton B, 40% in methanol, 2.9 mL, 6.95 mmol) in methanol (150 mL) was stirred at rt for 19 h. The mixture was evaporated under reduced pressure, and the residue was chromatographed on silica gel (hexane/ethyl acetate) to afford **5a** (8.11 g, 35% over two steps) as colorless prisms: mp 50−51 °C (from ether/hexane); IR (film, cm^{-1}) 1718, 1693; ^1H NMR (300 MHz, $CDCl_3$) δ 4.03−3.97 (m, 2H), 3.49−3.42 (m, 1H), 2.73−2.60 (m, 4H), 2.42−2.35 (m, 2H), 2.26−2.18 (m, 1H), 2.09 (s, 3H), 2.06−1.89 (m, 5H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 210.1, 206.9, 109.2, 72.0, 69.8, 63.9, 39.2, 38.5, 38.3, 38.0, 30.5, 29.9, 26.0, 25.5, 17.0; ES HRMS m/z ($C_{16}H_{24}O_5Na^+$) calcd 319.1516, obsd 319.1510; $[\alpha]^{21}_D$ −43.1 (c 1.67, benzene).

Typical Aldol Condensation Protocol Involving 5a and Proline Derivatives. A solution of **5a** (3.0 g, 10.1 mmol) in dimethyl sulfoxide (30 mL) was degassed under vacuum at rt for 10 min. After addition of proline derivative **20** (748 mg, 2.03 mmol), the mixture was heated at 50 °C with stirring for 16 h. After cooling, the mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, saturated $NaHCO_3$ solution, and brine. The organic phase was dried, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (ether/hexanes) to afford **7a** (1.60 g), a mixture of **6a** and **7a** (0.519 g), and pure **6a** (36 mg, total 2.155 g, 76%).

For **6a**: colorless needles; mp 59−60 °C (from ether hexanes); IR (film, cm^{-1}) 1710, 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (s, 1H), 4.19−3.97 (m, 2H), 3.51−3.35 (m, 1H) 2.84−2.38 (m, 6H), 2.24−1.89 (m, 4H), 1.81−1.51 (m, 2H), 1.36 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 198.5, 165.4, 126.6, 109,5, 72.0, 69.6, 53.3, 39.7, 38.3, 33.7, 32.2, 27.5, 26.7, 25.6, 23.1; ES HRMS m/z ($C_{16}H_{22}O_4^+$) calcd 278.1513, obsd 278.1501; $[\alpha]^{21}_D$ −57.7 (c 1.54, benzene).

For **7a**: colorless needles; mp 117−117.5 °C (from ether/hexanes); IR (film, cm^{-1}) 1709, 1662; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (d, J = 1.7 Hz, 1H), 4.12−4.04 (m, 2H), 3.51−3.44 (m, 1H), 2.91−2.75 (m, 2H), 2.55−2.25 (m, 5H), 2.23−2.10 (m, 3H), 1.96 (dd, J = 2.7, 14.7 Hz, 1H), 1.78−1.58 (m, 1H), 1.38 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 197.7, 165.3, 126.5, 109.5, 71.6, 69.5, 53.3, 39.3, 38.7, 33.2, 31.8, 26.6, 26.0, 25.2, 23.8; ES HRMS m/z ($C_{16}H_{22}O_4Na^+$) calcd 301.1410, obsd 301.1408; $[\alpha]^{21}_D$ −0.53 (c 1.5, benzene).

Compound 25b. A solution of **24b**[18] (1.0 g, 7.9 mmol), D-glyceraldehyde acetonide[19] (1.7 g, 13 mmol), and thiophenol (8 mL) in 50 mL of benzene was heated at reflux in the presence of 10 g of silica gel for 5 h. The reaction mixture was allowed to cool to rt and filtered. The solvent was removed, and the resulting oil was chromatographed on silica gel (ether/hexanes) to afford 2.57 g (93%) of **25b** as a pale yellow oil: IR (film, cm^{-1}) 1724, 1695; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51−7.10 (m, 5H), 4.60−3.40 (m, 4H), 2.67 (m, 4H), 1.93 (m, 4H), 1.50−1.10 (series of m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 107.2, 136.1, 129.4 (2C), 129.2 (2C), 77.8, 68.4, 66.2, 52.2, 44.6, 44.0, 26.8, 25.2, 24.9; ES HRMS m/z ($C_{19}H_{24}O_4SNa^+$) calcd 371.1295, obsd 371.1288. Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.49; H, 6.95. Found: C, 65.25; H, 6.83.

Compound 26b. Diketone **25b** (2.6 g, 7.5 mmol) was added to a large excess of Raney nickel (2 g) in 10 mL of ethanol. The mixture was stirred at rt for 1 h and filtered through Celite. The solvent was removed, and the resulting oil was chromatographed on silica gel (ether/hexanes) to afford 1.3 g (76%) of **26b** as a colorless oil: IR (film, cm^{-1}) 1724, 1697; ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (m, 1H), 3.96 (m, 2H), 3.47 (m, 1H), 2.66 (m, 2H), 2.48 (m, 2H), 2.15 (m, 3H), 1.58 (m, 3H), 1.35 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 205.3, 109.0, 73.4, 69.3, 62.9, 44.4, 43.9, 30.1, 26.8, 25.5, 25.0, 24.8; ES HRMS m/z ($C_{13}H_{20}O_4SNa^+$) calcd 263.1259, obsd 263.1259; $[\alpha]^{21}_D$ −24.0 (c 1.25, benzene).

Compound 5b. A solution of **26b** (7.39 g, 30.8 mmol), methyl vinyl ketone (5.1 mL, 61.6 mmol), and Triton B (1.3 mL, 3.08 mmol) in methanol (70 mL) was heated at reflux for 1 h. The solvent was removed under reduced pressure. The residue was diluted with ether, and the mixture was washed with water, saturated $NaHCO_3$ solution, and brine. The organic phase was dried, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (ether/hexanes) to afford **5b** (8.11 g, 85%): colorless needles; mp 79−82 °C; IR (film, cm^{-1}) 1716, 1694; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (m, 2H), 3.35 (t, J = 3.3 Hz, 1H), 2.45−1.70 (series of m, 17H), 1.20 (d, J = 2.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 211.6, 206.7, 109.2, 71.2, 69.5, 65.8, 41.8, 41.4, 37.3, 35.0, 29.8, 28.0, 27.9, 26.5, 25.3, 23.9; ES HRMS m/z ($C_{17}H_{26}O_5Na^+$) calcd 310.1780, obsd 310.1768. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.77; H, 8.47. Found: C, 65.55; H, 8.46.

Ring Closure of 5b Promoted by Pyrrolidine. A solution of **5b** (3.00 g, 12.9 mmol) in 50 mL of benzene was heated at reflux in the presence of pyrrolidine (1.00 mL, 12.9 mmol) for 1 h. Water was removed from the system via a Dean−Stark trap. The reaction mixture was concentrated and chromatographed on silica gel (ether/hexanes, 1/5) to afford 1.62 g of **7b**, 1.44 g of **6b**, and 0.456 g of a mixture (total of 93%) as an orange oil.

For **6b**: IR (CCl_4, cm^{-1}) 1706, 1667; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 1H), 4.51−4.42 (m, 1H), 4.20 (dd, J = 8.0, 6.0 Hz, 1H), 3.50 (t, J = 7.9 Hz, 1H), 2.85−2.65 (m, 2H), 2.53−2.42 (m, 2H); 2.39−1.83 (m, 6H), 1.75 (dd, J = 8.3, 14.8 Hz, 1H), 1.36 (s, 3H), 1.31 (s, 3H), 1.19−1.06 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 198.2, 166.4, 129.3, 109.3, 75.4, 70.3,

54.8, 40.4, 37.8, 35.3, 30.1, 31.5, 29.3, 27.7, 26.8, 25.8; ES HRMS *m/z* ($C_{17}H_{24}O_4Na^+$) calcd 292.1675, obsd 292.1720; $[\alpha]^{21}_D$ −60.0 (*c* 0.35, benzene).

For **7b**: IR (CCl_4, cm^{-1}) 1708, 1676; ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (s, 1H), 4.09−3.99 (m, 2H), 3.52−3.44 (m, 1H), 2.81 (ddd, J = 5.9, 13.3, 17.8 Hz, 1H), 2.74−2.65 (m, 1H), 2.57 (dd, J = 4.7, 12.7 Hz, 1H), 2.47−2.35 (m, 2H), 2.30−1.83 (m, 7H), 1.72−1.49 (m, 2H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 197.9, 164.7, 130.4, 109.2, 72.2, 70.1, 54.8, 40.5, 37.8, 36.48, 32.6, 31.86, 31.5, 27.1, 26.8, 25.8; ES HRMS *m/z* ($C_{17}H_{24}O_4Na^+$) calcd 292.1674, obsd 292.1800; $[\alpha]^{21}_D$ −40.0 (*c* 0.35, benzene).

Typical Aldol Condensation Protocol Involving 5b and Proline Derivatives. A solution of **5b** (1.04 g, 3.35 mmol) and **20** (1.36, 3.69 mmol) in methanol (20 mL) was heated to reflux for 2.5 h. The solvent was removed under reduced pressure, and the residue was diluted with ether. The mixture was washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (ether/hexanes) to afford **6b** (426 mg, 44%) as a colorless oil and **7b** (307 mg, 31%) as colorless crystals.

Controlled Hydride Reduction of 6b. A solution of **6b** (1.547 g, 5.3 mmol) in 10 mL of THF was added to a slurry of lithium aluminum hydride (0.442 g, 11.65 mmol) in 20 mL of THF at 0 °C. The mixture was stirred at rt for 1 h and 5 mL of water was carefully introduced. The mixture was added to 10 mL of ether and washed twice with 2 mL of brine. The organic layer was dried and the solvent was removed under reduced pressure. The resulting oil was treated with manganese dioxide (4.5 g, 51.8 mmol) at rt for 5 h. The mixture was filtered through Celite and the solvent was removed under reduced pressure. The resulting oil was chromatographed on silica gel (ether/hexanes, 1/1) to furnish 1.053 g (68%) of **27** as a white solid and 0.110 g (7%) of unreacted starting material.

For **27**: mp 116−118 °C; IR (CCl_4, cm^{-1}) 3450, 1668; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (s, 1H), 4.50 (m, 1H), 4.25 (m, 1H), 3.85 (dd, J = 6.3, 7.4 Hz, 1H), 3.49 (t, J = 7.4 Hz, 1H), 2.64 (m, 2H), 2.43 (dt, J = 5.5, 17 Hz, 1H), 2.34−1.40 (series of m, 12H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 172.6, 128.8, 109.2, 73.2, 73.0, 70.5, 46.1, 36.2, 33.9, 33.6, 31.4, 31.2, 29.7, 26.8, 25.9, 21.4; ES HRMS *m/z* ($C_{17}H_{26}O_4Na^+$) calcd 317.1723, obsd 317.1726; $[\alpha]^{20}_D$ −74.0 (*c* 0.35, benzene).

Silylated Cyanohydrin 28. To a stirred solution of **6a** (773 mg, 2.78 mmol) in CH_2Cl_2 (10 mL) were added potassium cyanide (27 mg, 0.42 mmol), 18-crown-6 as the CH_3CN complex (34 mg, 0.11 mmol), and trimethylsilyl cyanide (0.44 mL, 3.34 mmol) at 0 °C. After being stirred for 0.5 h at this temperature, the mixture was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (ether/hexanes) to afford **28** (601 mg, 57%) as colorless needles: mp 106−107 °C (from ether/hexanes); IR (film, cm^{-1}) 1669; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (s, 1H), 4.42−4.32 (m, 1H), 4.06 (dd, J = 6.1, 7.9 Hz, 1H), 3.45 (t, J = 7.7 Hz, 1H), 2.69−2.21 (m, 6H), 2.20−1.79 (m, 6H), 1.35 (s, 3H), 1.28 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 161.9, 128.4, 120.1, 109.3, 80.0, 72.9, 70.5, 46.7, 36.6, 34.5 (2C), 30.7, 28.9, 26.8, 25.5, 21.9, 1.2 (3C); ES HRMS *m/z* ($C_{20}H_{31}NO_4SiNa^+$) calcd 400.1915, obsd 400.1902; $[\alpha]^{21}_D$ −65.2 (*c* 1.62, benzene).

For the β-epimer of **28**: yield 75%; colorless needles; mp 108−108.5 °C (from ether/hexanes); IR (film, cm^{-1}) 1673; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (s, 1H), 4.10−3.98 (m, 2H), 3.45 (t, J = 7.3 H, 1H), 2.76 (ddd, J = 7.0, 11.9, 17.3 Hz, 1H), 2.60−2.20 (m, 5H), 2.15−1.80 (m, 6H), 1.39 (s, 3H), 1.28 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 159.6, 130.0, 120.2, 109.3, 80.2, 72.1, 70.3, 47.1, 35.6, 34.3, 34.2, 30.8, 29.4, 26.9, 25.9, 22.0, 1.2 (3C); ES HRMS *m/z* ($C_{20}H_{31}NO_4SiNa^+$) calcd 400.1915, obsd 400.1910; $[\alpha]^{21}_D$ +3.0 (*c* 1.67, benzene).

Hydride Reduction of 28. To a stirred suspension of lithium aluminum hydride (242 mg, 6.38 mmol) in THF (10 mL) was added **28** (601 mg, 1.59 mmol) dissolved in THF (5 mL) at 0 °C. After 10 min of stirring, the mixture was heated at reflux for 2.5 h, water was carefully introduced, and stirring was resumed for 2 h at rt. The mixture was filtered through a Celite pad, and the filtrate was extracted with ethyl acetate. The combined organic layers were dried and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (methanol/ethyl acetate/NH_4OH) to afford a diastereomeric mixture of **29** (146 mg, 30%) and diol **30** (233 mg, 52%), both as colorless oils. Amine **29** and diol **30** were used in subsequent reactions without further purification of diastereomers.

Ring Expansion of 29. To a stirred suspension of **29** (146 mg, 0.47 mmol) in glacial acetic acid (2 mL) and water (2 mL) was added sodium nitrite (100 mg, 1.41 mmol) at 0 °C. After being stirred for 2 h, the mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL), and manganese dioxide (366 mg, 4.22 mmol) was added at rt. After 1.5 h of stirring at this temperature, the mixture was chromatographed on silica gel (ether/hexanes) to afford **6b** (3 mg, 2%), **32** (71 mg, 58%), and **33** (24 mg, 19%). The spectra of **6b** were identical to those recorded for the material prepared from **5b**.

For **32**: colorless oil; IR (film, cm^{-1}) 1702, 1668; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (s, 1H), 4.25−4.12 (m, 1H), 4.08 (dd, J = 6.0, 7.8 Hz, 1H), 3.44 (t, J = 7.7 Hz, 1H), 3.03 (d, J = 12.0 Hz, 1H), 2.69−2.33 (m, 7H), 2.29−1.96 (m, 3H), 1.88−1.60 (m, 3H), 1.38 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 198.8, 169.3, 128.4, 109.4, 72.1, 69.9, 50.1, 43.8, 40.7, 39.6, 33.7, 33.5, 32.4, 26.7, 25.7, 24.7; ES HRMS *m/z* ($C_{17}H_{24}O_4Na^+$) calcd 315.1567, obsd 315.1578; $[\alpha]^{21}_D$ −113.8 (*c* 1.12, benzene).

For **33**: colorless oil; IR (film, cm^{-1}) 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (d, J = 1.7, 1H), 4.47 (ddd, J = 3.6, 7.5, 13.6 Hz, 1H), 4.15 (dd, J = 6.0, 8.0 Hz, 1H), 3.51 (t, J = 7.9 Hz, 1H), 2.98 (dd, J = 2.2, 4.1 Hz, 1H), 2.62−2.49 (m, 2H), 2.42−1.91 (m, 8H), 1.75−1.50 (m, 3H), 1.37 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 167.0, 126.2, 109.0, 72.6, 70.3, 63.4, 50.1, 42.1, 38.1, 34.1, 32.1, 31.4, 26.9, 26.0, 25.6, 23.8; ES HRMS *m/z* ($C_{17}H_{24}O_4Na^+$) calcd 315.1567, obsd 315.1554; $[\alpha]^{21}_D$ −80.1 (*c* 1.10, benzene).

For the β-epimer of **32**: 63% yield; colorless prisms; mp 120−121 °C (from ether); IR (film, cm^{-1}) 1699, 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 1H), 4.22−4.13 (m, 1H), 4.06 (dd, J = 5.9, 7.8 Hz, 1H), 3.45 (t, J = 7.8 Hz, 1H), 3.06 (d, J = 12.4 Hz, 1H), 2.68−2.32 (m, 7 H), 2.28−2.10 (m, 2H), 1.98 (dt, J = 4.6, 14.1 Hz, 1H), 1.92−1.76 (m, 2H), 1.73−1.51 (m, 1H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 197.9, 169.2, 128.3, 109.3, 72.0, 69.8, 50.9, 43.5, 41.2, 38.8, 33.4, 32.7, 31.1, 26.7, 25.6, 25.3; ES HRMS *m/z* ($C_{17}H_{24}O_4Na^+$) calcd 315.1567, obsd 315.1578; $[\alpha]^{21}_D$ +141.6 (*c* 1.67, benzene).

For the β-epimer of **33**: 13% yield; colorless oil; IR (film, cm^{-1}) 1672; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (d, J = 1.8 Hz, 1H), 4.34−4.25 (m, 1H), 4.10 (dd, J = 5.8, 7.8 Hz, 1H), 3.45 (t, J = 7.9 Hz, 1H), 2.95 (dd, J = 2.0, 4.1 Hz, 1H), 2.97−2.20 (m, 7H), 2.04−1.94 (m, 2H), 1.91−1.69 (m, 2H), 1.68−1.50 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.42−1.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 165.7, 126.7, 108.4, 72.4, 70.0, 63.1, 50.7, 41.9, 37.2, 33.8, 31.8, 30.7, 26.7, 26.0, 25.8, 23.7; ES HRMS *m/z* ($C_{17}H_{24}O_4Na^+$) calcd 315.1567, obsd 315.1587; $[\alpha]^{21}_D$ +87.3 (*c* 1.72, benzene).

For **6b**: 2% yield; all of the spectra proved identical to those recorded for the keto alcohol prepared from **5b**.

Compound 31. To a stirred suspension of **30** (56 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) was added manganese dioxide (173 mg, 2.0 mmol) at rt. After 1.5 h of stirring at this temperature, the mixture was filtered through a Celite pad and the filtrate

was evaporated under reduced pressure. The residue was chromatographed on silica gel (hexanes/ethyl acetate) to afford **31** (41 mg, 74%).

For **31**: colorless oil; IR (film, cm^{-1}) 3347, 1652; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (d, J = 1.3 Hz, 1H), 4.41(quint, J = 7.0 Hz, 1H), 4.09 (dd, J = 6.0, 7.9 Hz, 1H), 3.53 (dd, J = 5.2, 10.7 Hz, 1H), 3.49 (t, J = 8.0 Hz, 1H), 2.63−2.33 (m, 4H), 2.18−2.16 (m, 1H), 2.08−1.70 (m, 7H), 1.36 (s, 3H), 1.30 (s, 3H), 1.50−1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 167.8, 126.2, 109.1, 78.5, 73.4, 70.7, 44.0, 35.7, 34.0, 32.5, 31.4, 30.1, 26.8, 25.6, 23.9; ES HRMS *m/z* ($C_{16}H_{24}O_4Na^+$) calcd 303.1567, obsd 303.1565; $[\alpha]^{21}_D$ −120.5 (*c* 0.80, benzene).

For the β-epimer of **31**: 84% yield; colorless oil; IR (film, cm^{-1}) 3442, 1661; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (d, J = 1.7 Hz, 1H), 4.38−4.29 (m, 1H), 4.13 (dd, J = 6.0, 8.2 Hz, 1H), 3.54 (t, J = 8.0 Hz, 1H), 3.35 (dd, J = 4.0, 10.9 Hz, 1H), 2.51−2.11 (m, 7H), 2.07−1.73 (m, 4H), 1.65 (dd, J = 0.7, 15.2 Hz, 1H), 1.58−1.35 (m, 1H), 1.46 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 168.0, 125.6, 110.2, 78.0, 72.0, 70.2, 44.6, 34.6, 33.5, 31.8, 30.1, 29.7, 26.8, 25.8, 24.1; ES HRMS *m/z* ($C_{16}H_{24}O_4Na^+$) calcd 303.1567, obsd 303.1575; $[\alpha]^{21}_D$ +74.0 (*c* 0.50, benzene).

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Supporting Information Available: ORTEP diagrams and tables of X-ray crystal data, atomic coordinates, both lengths and angles, equivalent isotropic and anisotropic displacement parameters, and intramolecular hydrogen bonds for **27**. High-field ^1H and ^{13}C NMR spectra for all compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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