in. *p*-Dioxane (16.0 μL) and *m*-bromobenzotrifluoride (35.0 μL) were used as internal standards, and the [MPA] values were determined by using ^1H and ^{19}F NMR as given in Table VII. Use of temperature-variable ^1H NMR at 100 MHz allowed the determined of [MFA] at 0 and 50 °C. In similar but separate experiments, the [MFA] value was shown to be constant in all of the solvents of Table III.

Ultraviolet Spectrum of *N*-Methyl-*C*-phenylnitrone in Different Solvents. The UV of 1a was taken in several spectro-grade solvents as shown in Table VIII. The spectra were taken in the absorbance mode from 240 to 500 nm and from 0 to 1.5 absorbance units. The concentration of the nitrone used for the UV studies was uniformly 5.9×10^{-5} M. There were no other UV bands observed.

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The Use of Cysteine- and Serine-Derived Thiazolidinethiones and Oxazolidinethiones as Efficient Chiral Auxiliaries in Aldol Condensations

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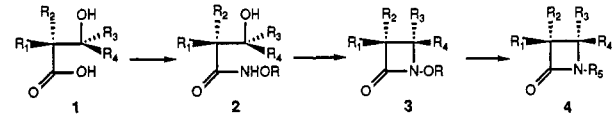
Cysteine-derived thiazolidinethiones and serine-derived oxazolidinethiones serve as efficient chiral auxiliaries in boron- and tin-mediated aldol condensations. The condensations with a variety of simple aldehydes produced the expected erythro products in high chemical and optical yields. Additional advantages of these chiral auxiliaries were the ease of removal by methanolysis or hydroxaminolysis and their practical recyclability.

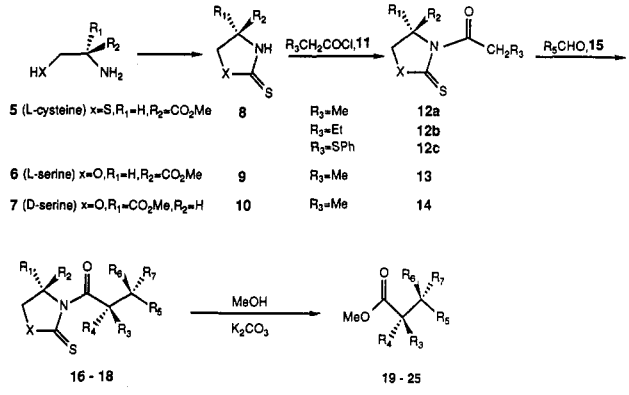
Extensive studies by Evans and co-workers,[1] Heathcock and co-workers,[2] Masamune and Choy,[3] Mukaiyama and co-workers,[4] and others[5] have illustrated the utility of diastereoselective and enantioselective aldol condensations for the synthesis of a number of β-hydroxy carbonyl containing compounds. However, with the intent of designing very efficient and practical routes to β-lactam antibiotics by the hydroxamate approach (Scheme I)[6] and other biologically important molecules, we established several additional criteria for the assembly of appropriate carbon frameworks by asymmetric aldol condensations. Ideally, such asymmetric reactions should employ chiral auxiliaries that are readily available and readily acylated, promote efficient enantioselective carbon–carbon bond formation, and can be easily removed by solvolysis or aminolysis. The ability to recycle the chiral auxiliary, to visually monitor certain parts of the reaction sequence, and to easily control formation of *either* optical antipode of the expected erythro aldol product were also desirable.

We were especially attracted to the use of acylthiazolidinethiones for aldol condensations because the acylthiazolidinethione also serves as an effective active ester for subsequent elaboration.[7] This fact had encouraged us to use Mukaiyama's tin-mediated aldol condensation of nonchiral acylthiazolidinethiones[4e] in a stereoselective synthesis of β-lactams.[8] While chiral versions of tin enolate chemistry using chiral diamines[4b,f] have been reported, we were interested in incorporating the chirality into the thiazolidinethione itself. The ready availability of optically pure 4(*R*)-(methoxycarbonyl)-1,3-thiazolidine-2-thione (8)[9] from cysteine **5** and the reported ease of aminolysis (with chiral recognition and visual monitoring)[9] of the corresponding acylated derivatives made consideration of it, and of the related serine-derived oxazolidinethiones **9** and **10**, very attractive for use as chiral auxiliaries in aldol condensations (Scheme II). The high

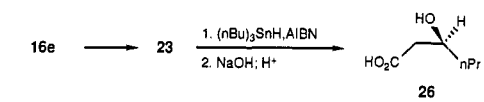
Scheme I



Scheme II



Scheme III



enantioselectivity of aldol reactions of chiral boron enolates[1] also prompted us to study the boron enolates of

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Table I. Aldol Products and the Corresponding Methyl Esters

compd	yield, %	X	R_1	R_2	R_3	R_4	R_5	R_6	R_7	compd	yield, %	% ee[a]
16a	76	S	H	CO_2Me	Me	H	Ph	OH	H	**19**	95	97
16b	87	S	H	CO_2Me	Me	H	*i*-Pr	OH	H	**20**	92	97
16c	90	S	H	CO_2Me	Et	H	Ph	OH	H	**21**	85	96
16d	85	S	H	CO_2Me	Et	H	*i*-Pr	OH	H	**22**	85	99
16e	87	S	H	CO_2Me	SPh	H	*n*-Pr	OH	H	**23**	82	*b*
17a	89	O	H	CO_2Me	Me	H	Ph	OH	H	**19**	67	98
17b	81	O	H	CO_2Me	Me	H	*i*-Pr	OH	H	**20**	60	98
18a	78	O	CO_2Me	H	H	Me	Ph	H	OH	**24**	73	98
18b	83	O	CO_2Me	H	H	Me	*i*-Pr	H	OH	**25**	58	99

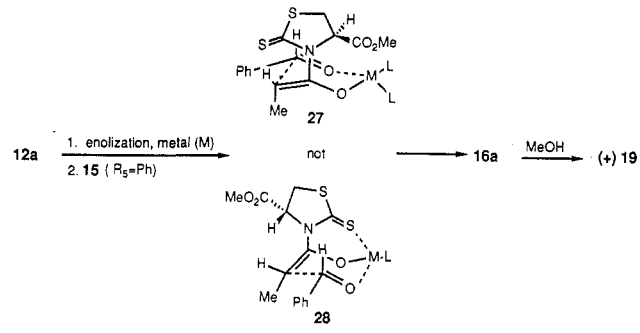
[a] % ee was determined by comparison of the optical rotation with values reported in the literature or more accurately by chiral NMR shift studies. (See Experimental Section.) [b] 99% ee based on the carboxylic acid **26**.

chiral acylthiazolidine- and acyloxazolidinethiones **12–14**. However, the usual oxidative workup employed in boron-mediated aldol condensations was anticipated to be incompatible with our sulfur-containing chiral auxiliaries. Herein we describe in detail the development of enantioselective aldol condensations based on enolates derived from cysteine- and serine-derived acylthiazolidine- and acyloxazolidinethiones.

Results and Discussion

The thiazolidinethione **8** was prepared by the reaction of L-cysteine methyl ester (**5**) hydrochloride and carbon disulfide as previously described.[9] Acylation of **8** with acid chlorides **11** proceeded as expected to produce the yellow acylated chiral auxiliaries **12a–c** in over 90% yields. These substrates proved to be completely compatible with the usual di-*n*-butylboron triflate mediated aldol conditions with the exception that *no oxidative workup was required.* Simply quenching the reaction with pH 7 phosphate buffer, followed by extractive workup and chromatography, provided the desired erythro aldol products **16** cleanly and in good yields. The aldol products usually consisted of a single erythro diastereomer within high-field-NMR detection limits. Methanolysis of the yellow aldol products **16a–d** provided the corresponding known colorless optically active methyl esters **19–22** for comparison of optical purity. Methanolysis of the thiophenyl derivative **16e** to **23** was followed by reductive desulfurization with $(n\text{-Bu})_3SnH$ and hydrolysis to provide the known β-hydroxy acid **26** (Scheme III) in high optical purity (~99% ee). As

Scheme IV



can be seen in Table I, the aldol condensations and methanolyses generally proceeded in excellent chemical yield and provided the final esters in 96% to greater than 99% enantiomeric excess. Thus, the aldol condensations based on the acylthiazolidinethiones satisfied most of the criteria established earlier.

The preliminary success with the development of an efficient process for effecting chiral aldol condensations encouraged us to consider the remaining question of whether the same or a similar aldol condensation could be used to eventually provide the enantiomeric β-hydroxy carbonyl systems; that is, the mirror images of esters **19–22**. Two approaches to solving this problem were considered. One approach was to simply start with the opposite optical isomer of the chiral auxiliary (D-cysteine derivative instead of L-cysteine derivative **5**). The other was to retain the same chiral auxiliary, but change the selectivity of the aldol condensation by effecting changes in the transition state. Assuming that the aldol condensations described above proceed by the usually postulated pericyclic transition state **27** (M = boron, Scheme IV) and that the chiral auxiliary must be orientated as shown to account for the formation of the products that were obtained, changing of the metal to one that might also be able to chelate to the thiocarbonyl of the chiral auxiliary would necessitate a rotation of the auxiliary. The resulting "ate" complex **28** should eventually react to provide aldol products resulting from opposite facial selectivity of the enolate. Since our previous experience indicated that stannous triflate successfully mediated aldol condensations of nonchiral acylthiazolidinethiones,[8] we decided to test the effects of using tin enolates derived from the chiral derivative **12a**. Interestingly, attempted generation of the tin enolate at −78 °C and reaction with benzaldehyde resulted in no reaction. However, at −20 °C for 90 min the same reaction produced an aldol product identical with **16a**, which had been produced by the boron enolate process. Subsequent methanolysis provided the ester (+)-**19** with essentially the same optical rotation as the compound produced through the boron-initiated route. This result suggested that, in this case, the stannous triflate mediated aldol condensation also

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proceeds through a transition state similar to **27** (M = Sn) and does not involve chelation of the thione portion of the chiral auxiliary as shown in **28** (M = Sn). Subsequent to our initial studies in this area, other workers have described stannous triflate mediated aldol and related condensation reactions with similar acylthiazolidinethiones that reportedly provided products consistent with the chelated transition state **28**.[10] Still more recently, Abdel-Magid et al.[5a] provided a systematic study of the effects of various metals on the outcome of aldol condensation reactions of acylated chiral auxiliaries and indicate that, as with our results, both boron- and tin(II)-mediated reactions provide products consistent with the nonchelated transition state. However, the use of other metals, including tin(IV), provides aldol products apparently derived from the chelated transition state. Further studies of enolate formation and aldol condensation of our acylthiazolidinethiones with these and different metals are under consideration.

Our second approach to providing access to the enantiomeric β-hydroxy carbonyl systems (i.e. (−)-**19**) involved changing the configuration of the chiral auxiliary. Conceptually this could have easily been done by simply using D-cysteine instead of L-cysteine in the previous sequence (Scheme II). The high cost of D-cysteine encouraged us to find an alternative. Since D-serine **7** is relatively inexpensive, we decided to study the aldol chemistry of the corresponding L- and D-serine-derived acyloxazolidinethiones **13** and **14** (Scheme II). We were initially concerned that even simple changes in the nature of the chiral auxiliary from thione **5** to **6** or **7** might have a detrimental effect on the aldol process. However, as shown in Table I, the aldol reactions of the L-serine-derived acyloxazolidinethione **13** provided the condensation products **17a,b** as desired. During the formation of **17a**, a small amount of a chromatographically faster moving component was detected. This component was isolated and was found to be the other erythro aldol product. By careful isolation, in this case, the diastereoselectivity of the aldol process was determined to be >96% in favor of the expected erythro isomer **17a**. None of the corresponding threo products were detected. Methanolysis of **17a,b** provided the same methyl esters, **19** and **20**, with comparably high enantiomeric purity, that had been obtained from the cysteine-derived aldols. The only drawback was that the methanolysis product yields were consistently lower from displacement of the serine-derived chiral auxiliary. Preparation and aldol condensation reactions of the D-serine-derived thiones **14** also proceeded as expected. Subsequent methanolysis of the aldol products **18a,b** produced β-hydroxy esters **24** and **25**, which were identical with **19** and **20** in very respect, except for the optical rotation, which had the opposite sign. Thus, both enantiomers of erythro aldol products are conveniently available by appropriate choice of these amino acid based thione chiral auxiliaries.

Applications of these and related aldol condensations to the preparation of the carbon framework of optically active bicyclic β-lactams have been described.[11,12] The facile and visually monitored hydroxaminolyses of the appropriate acylthiazolidinethiones **29** are especially noteworthy since they provide direct access to hydroxamate precursors of bicyclic β-lactams like PS-5 (**32**, Scheme V).

Experimental Section

General Comments. Melting points were taken on either a Fisher-Johns or a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 727B and 1420 spectrometers. Proton NMR spectra were obtained in deuteriochloroform with tetramethylsilane as an internal standard on Varian EM 390, Magnachem A-200, and Nicolet NB 300 NMR spectrometers. Mass spectra were recorded on an AEI MS902 or a Dupont DP-1 mass spectrometer. Optical rotations were measured with a Rudolf Research Autopol III automatic polarimeter. Radial chromatography was performed by using a Chromatotron Model 7924 instrument purchased from Harrison Research Inc., Palo Alto, CA. TLC was carried out by using aluminum-backed silica gel 60 F-254 (0.2-mm plates). Gas chromatographic analyses were performed with a Hewlett-Packard 5890 gas chromatograph on a 0V-1 column. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

4(*R*)-(Methoxycarbonyl)-1,3-thiazolidine-2-thione (8).[10,13] To a suspension of L-cysteine methyl ester (**5**) hydrochloride (2.0 g, 11.66 mmol) in methylene chloride (20 mL) under nitrogen at room temperature was added triethylamine (2.0 mL, 14.35 mmol) followed by addition of carbon disulfide (740 μL, 12.3 mmol). The suspension turned yellow instantaneously, but it slowly faded over 10 min to a much lighter yellow solution. The reaction mixture was stirred at room temperature overnight. Evaporation of solvent gave a white solid residue, which was suspended in ethyl acetate and filtered through a short silica gel column (60–200 mesh, 10 cm, eluting with ethyl acetate). The filtrate was concentrated under vacuum and separated on a chromatotron using silica and eluting with ethyl acetate–hexanes (1:4) to provide 1.796 g (87%) of **8** as a light yellow oil: ^{1}H NMR (90 MHz) δ 3.85 (d, 2 H, J = 7.5 Hz), 3.90 (s, 3 H), 4.85 (t, 1 H, J = 7.5 Hz), 7.8–8.3 (br, 1 H); IR (neat) 3150–3350, 1750, 1465, 1220, 1040 cm^{-1}; R_f 0.5 (silica gel, ethyl acetate–hexanes, 1:1); $[\alpha]_D$ −64.5° (c 1.50, $CHCl_3$) [lit.[13] $[\alpha]_D$ −64.5° (c 1.50, $CHCl_3$)].

4(*S*)-(Methoxycarbonyl)-1,3-oxazolidine-2-thione (9). To a suspension of L-serine methyl ester (**6**) hydrochloride (6.5 g, 41.8 mmol) in 50 mL of tetrahydrofuran (THF) at room temperature was added triethylamine (4.23 g, 41.8 mmol), followed by the addition of 25 mL of carbon disulfide. The resulting suspension was refluxed overnight. Methylene chloride (100 mL) was added, and the organic solution was washed with aqueous 5% oxalic acid, dried over $MgSO_4$, filtered, and concentrated to provide crude **9** as an orange-yellow oil. Column chromatography on silica gel eluting with ethyl acetate–hexanes (1:2) provided 4.32 g (63%) of pure **9** as an oil: ^{1}H NMR (90 MHz) δ 3.96 (s, 3 H), 5.01 (m, 3 H), 8.98 (br, 1 H); IR (neat) 3260, 2950, 1745 cm^{-1}; mass spectrum (CI with isobutane), m/e 162 (M + 1); $[\alpha]_D$ −16° (c 6.27, $CHCl_3$).

4(*R*)-(Methoxycarbonyl)-1,3-oxazolidine-2-thione (10) was prepared in 71% yield by using the same procedure as for its optical isomer **9**. Except for the opposite sign of the rotation, the spectral data were also identical with those obtained for **9**.

***N*-Propionyl-4(*R*)-(methoxycarbonyl)-1,3-thiazolidine-2-thione (12a).** To a solution of **8** (20.2 g, 113.9 mmol) in 150 mL of methylene chloride at −78 °C under nitrogen was added 10.5 mL (129.8 mmol) of pyridine. After the mixture was stirred for 5 min, a solution of propionyl chloride (12.0 mL, 138.1 mmol) in 10 mL of methylene chloride was added dropwise. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to room temperature over 30 min, and then stirred overnight. TLC analysis indicated the total disappearance of **8**. More methylene chloride (400 mL) was added, and the reaction mixture was extracted with water, with 5% aqueous oxalic acid, and again with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The oily dary yellow residue was chromatographed on silica gel using ethyl acetate–hexanes (1:8) to provide 24.6 g (91% yield) of **12a** as a light yellow oil, which solidified upon standing. Recrystallization from ethyl acetate–hexanes gave yellow needles: mp 62–63 °C; ^{1}H NMR (300 MHz) δ 1.15 (t, 3 H, J = 7.5 Hz),

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3.50 (dd, 2 H, J = 7.5 Hz, J = 7.5 Hz), 3.65 (q, 2 H, J = 7.5 Hz), 3.80 (s, 3 H), 5.70 (dd, 1 H, J = 7.5 Hz, J = 7.5 Hz); IR (neat oil before recrystallization) 1750, 1710, 1160, 1050 cm^{-1}; mass spectrum, m/e 233 (M^+); R_f 0.46 (ethyl acetate–hexanes, 1:3); $[\alpha]_D$ −127° (c 0.98, $CHCl_3$). Anal. Calcd for $C_8H_{11}NO_3S_2$: C (41.18), H (4.75), N (6.00), S (27.48). Found: C (41.32), H (4.81), N (5.87), S (27.34).

***N*-Butyryl-4(*R*)-(methoxycarbonyl)-1,3-thiazolidine-2-thione (12b)** was prepared in 97% yield from butyryl chloride and **8** by the same procedure described for **12a**: mp 53–54 °C (yellow needles from ethyl acetate–hexanes, 1:4); ^1H NMR (90 MHz) δ 0.95 (t, 3 H, J = 7.5 Hz), 1.65 (q, 2 H, J = 7.5 Hz), 2.90–3.75 (m, 4 H), 3.80 (s, 3 H), 5.65 (dd, 1 H, J = 7.5 Hz, J = 7.5 Hz); IR 1750, 1700, 1210, 1150, 770 cm^{-1}; mass spectrum, m/e 247 (M^+); R_f 0.3 (ethyl acetate–hexanes, 1:4); $[\alpha]_D$ −124° (c 1.87, $CHCl_3$). Anal. Calcd for $C_9H_{13}NO_3S_2$: C (43.71), H (5.29), N (5.66), S (25.93). Found: C (43.91), H (5.24), N (5.45), S (26.01).

***N*-[(Phenylthio)acetoxy]-4(*R*)-(methoxycarbonyl)-1,3-thiazolidine-2-thione (12c)** was prepared in the same manner in 90% yield from thiophenoxyacetyl chloride and **8**: mp 71–72 °C (yellow needles from ether–hexanes, 3:1); ^1H NMR (90 MHz) δ 3.55 (dd, 2 H, J = 7.5 Hz, J = 7.5 Hz), 3.80 (s, 3 H), 4.75 (dd, 2 H, J = 7.5 Hz, J = 15 Hz), 5.60 (dd, 1 H, J = 7.5 Hz, J = 7.5 Hz), 7.1–7.6 (m, 5 H); IR (KBr) 1755, 1700, 1210, 1050, 745, 695 cm^{-1}; mass spectrum (CI with isobutane), m/e 328 (M + 1); R_f 0.34 (ethyla cetate–hexanes, 1:3); $[\alpha]_D$ −59° (c 2.12, $CHCl_3$). Anal. Calcd for $C_{13}H_{13}NO_3S_3$: C (47.68), H (4.00), N (4.27), S (29.37). Found: C, (47.76), H (4.15), N (4.17), S (29.11).

3-Propionyl-4(*S*)-(methoxycarbonyl)-1,3-oxazolidine-2-thione (13) was prepared in 97% yield from **9** and propionyl chloride by using the same procedure: mp 61–62 °C; ^1H NMR (300 MHz) δ 1.27 (t, 3 H), 3.45 (m, 2 H), 3.94 (s, 3 H), 4.57–5.43 (m, 3 H). Addition of 20 mol % of tris[3-[(heptafluoropropyl)-hydroxymethylene]-*d*-camphorato]europium(III) ($Eu(hfc)_3$ revealed the presence of none of the other enantiomer (**14**) within the limits of NMR detection (<0.5%), as determined by performing the same type of shift study on an intentionally prepared mixture of **13** and **14**. IR (neat oil before recrystallization): 2970, 1750, 1710 cm^{-1}. Mass spectrum (CI with isobutane): m/e 217 (M^+), 218 (M + 1). $[\alpha]_D$: −39° (c 1.01, $CHCl_3$). Anal. Calcd for $C_8H_{11}O_4NS$: C (44.23), H (5.10), N (6.45). Found: C (44.45), H (5.25), N, (6.48).

3-Propionyl-4(*R*)-(methoxycarbonyl)-1,3-oxazolidine-2-thione (14) was prepared in 96% yield from **10** and propionyl chloride in the same manner: mp 61–62 °C (after recrystallization from chloroform–hexanes). All of the spectral data were identical with those of **13** except the NMR with the added chiral shift agent, which displayed a significant shift of the methyl ester singlet. $[\alpha]_D$ +36° (c 1.14, $CHCl_3$). Although the rotation is of the opposite sign as expected, we could not account for the 3-deg difference in the rotation between **13** and **14**. Again, chiral shift NMR studies revealed none of **13** in the sample of **14**, within the limits of detection of <0.5% determined by "spiking" the samples with their enantiomers in the shift study. Anal. Calcd for $C_8H_{11}O_4NS$: C (44.23), H (5.10), N (6.45). Found: C (44.28), H (4.96), N (6.50).

General Procedure for the Aldol Condensation. Preparation of 16a. To a stirred solution of **12a** (569 mg, 2.44 mmol) in 10 mL of methylene chloride *at 0 °C (internal temperature)* under nitrogen was added dibutylboryl trifluoromethanesulfonate (2.6 mmol, 2.6 mL of a 1.0 M solution in methylene chloride, Aldrich). Note that use of large excesses (>200 mol %) of $(n\text{-}Bu)_2B(OTf)$ was detrimental. After the mixture was stirred for 5 min at 0 °C, diisopropylethylamine (440 μL, 2.53 mmol) was added portionwise with a microsyringe. *The internal temperature was carefully mantained at 0 °C during this process.* Lower or higher temperatures decreased the diastereoselectivity of the condensation. The resulting light yellow solution was stirred at 0 °C for another 30 min and then cooled to −78 °C, and benzaldehyde (273 μL, 110 mol % relative to **12a**) was added by syringe. The reaction mixture was stirred for 30 min at −78 °C and then allowed to warm to 0 °C over 20 min. At this time, little or no starting material (**12a**) could be detected by TLC analysis. A pH 7 phosphate buffer (10 mL) was added, and the mixture was stirred vigorously at 0 °C for 3 min. The yellow methylene chloride solution was separated, concentrated, and filtered through a silica gel column with ethyl acetate as the eluant to remove the boric acid byproducts. The filtrate was concentrated under reduced pressure and purified on the chromatotron using ethyl acetate–hexanes (1:4) to provide 629 mg (76% yield) of **16a** as a light yellow solid. Recrystallization from ether–hexanes (1:2) provided the analytical sample: mp 134–135 °C; ^1H NMR (300 MHz) δ 1.32 (d, 3 H, J = 6.9 Hz), 2.71 (d, 1 H, J = 3 Hz), 3.17–3.20 (m, 2 H, J = 1.5 Hz, J = 5.7 Hz), 3.80 (s, 3 H), 4.82 (dq, 1 H, J = 6.3 Hz, J = 6.9 Hz), 4.92 (dd, 1 H, J = 6.3 Hz, J = 3 Hz), 5.10 (dd, 1 H, J = 3 Hz, J = 5.7 Hz), 7.20–7.40 (m, 5 H); IR (Nujol) 3520, 1740, 1700, 1240, 1030, 700 cm^{-1}; mass spectrum, m/e 321 (M − H_2O); $[\alpha]_D$ −104° (c 2.64, $CHCl_3$). Anal. Calcd for $C_{15}H_{17}NO_4S_2$: C (53.07), H (5.04), N (4.12), S (18.89). Found: C (52.96), H (4.88), N (3.99), S (19.06).

The aldol condensation between **12a** and benzaldehyde was repeated by using tin triflate instead of the dibutylboryl triflate. Thus, to a suspension of tin triflate (1.74 g, 4.18 mmol) in 10 mL of methylene chloride at −78 °C under nitrogen was added diisopropylethylamine (650 μL, 3.73 mmol). After the mixture was stirred for 10 min at −78 °C, the suspension turned light yellow. A solution of **12a** (650 mg, 2.79 mmol) in methylene chloride (3 mL) was added, and the mixture was stirred for 3 h while the temperature was maintained between −40 and −50 °C. The mixture was cooled to −78 °C, and a solution of benzaldehyde (425 μL, 150 mol % relative to **12a**) in 1 mL of methylene chloride was added. Stirring was continued for 40 min, but TLC analysis of an aliquot indicated that no reaction occurred. Therefore, the temperature was raised to −20 °C and maintained there for 90 min, after which time only a trace of **12a** was detected on TLC analysis. The reaction was quenched by adding excess pH 7 phosphate buffer, and the resulting mixture was stirred vigorously at room temperature for 3 min. More methylene chloride (150 mL) was added, and the suspension was filtered through Celite. The methylene chloride layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The oily residue was purified by column chromatography (silica gel, ethyl acetate–hexanes, 1:4) to provide the aldol product **16a** (430 mg, 71% yield) as a light crystalline solid with all properties identical with those obtained by the boron enolate process.

The following aldol products were formed by using the boron enolate process.

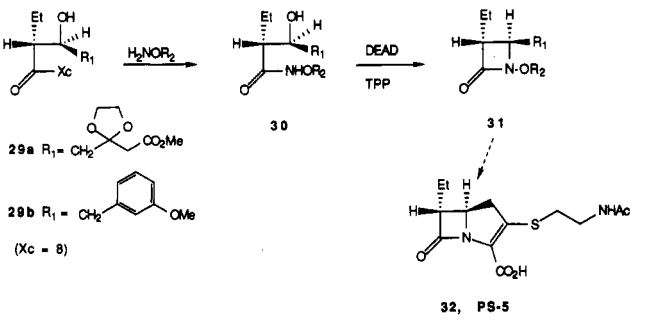
Aldol product 16b was formed from **12a** and isobutyraldehyde as a light yellow oil in 87% yield: ^1H NMR (300 MHz) δ 0.88 (d, 3 H, J = 6.6 Hz), 1.20 (d, 3 H, J = 6.6 Hz), 1.24 (d, 3 H, J = 6.9 Hz), 1.67 (heptet, 1 H, J = 6.6 Hz), 2.63 (br s, 1 H), 3.37 (dd, 1 H, J = 1.8 Hz, J = 12 Hz), 3.57 (br d, 1 H, J = 8.4 Hz), 3.70 (dd, 1 H, J = 12 Hz, J = 8.4 Hz), 3.83 (s, 3 H), 4.78 (dq, 1 H, J = 6.9 Hz, J = 3 Hz), 5.64 (dd, 1 H, J = 8.4 Hz, J = 1.8 Hz); IR (neat) 3480, 1750, 1700 cm^{-1}; mass spectrum (CI with isobutane), m/e 306 (M + 1); $[\alpha]_D$ −55° (c 3.09, $CHCl_3$).

Aldol product 16c was formed from **12b** and benzaldehyde as a light yellow solid in 90% yield: mp 120–121 °C (yellow needles from ether–hexanes, 1:1); ^1H NMR (300 MHz) δ 0.92 (t, 3 H, J = 7.5 Hz), 1.87 (m, 2 H), 2.40 (d, 1 H, J = 3 Hz), 2.87 (dd, 1 H, J = 12 Hz, J = 2 Hz), 3.04 (d, 1 H, J = 12 Hz), 3.65 (s, 3 H), 4.75 (dd, 1 H, J = 7.5 Hz, J = 3 Hz), 5.03 (dd, 1 H, J = 8 Hz, J = 2 Hz), 5.21 (dd, 1 H, J = 7.5 Hz, J = 6 Hz), 7.2–7.4 (m, 5 H); IR (KBr) 3540, 1740, 1700, 1250, 1040, 700 cm^{-1}; mass spectrum, m/e 353 (M^+); R_f 0.25 (ethyl acetate–hexanes, 1:2). Anal. Calcd for $C_{16}H_{19}NO_4S_2$: C (54.37), H (5.41), N (3.96), S (18.14). Found: C (54.03), H (5.46), N (3.82), S (17.88).

Aldol product 16d was formed from **12b** and isobutyraldehyde as a light yellow oil in 85% yield: ^1H NMR (300 MHz) δ 0.90 (d, 3 H, J = 7.5 Hz), 1.00 (d, 3 H, J = 7.5 Hz), 1.05 (t, 3 H, J = 7.5 Hz), 1.60–2.00 (m, 3 H), 2.21 (d, 1 H, J = 3 Hz), 3.35 (dd, 1 H, J = 1.8 Hz, J = 12 Hz), 3.52 (ddd, br, 1 H), 3.67 (dd, 1 H, J = 12 Hz, J = 8.4 Hz), 3.83 (s, 3 H), 5.09 (dt, 1 H, J = 9.5 Hz, J = 3.9 Hz), 5.67 (dd, 1 H, J = 8.4 Hz, J = 1.8 Hz); IR (neat) 3460, 1740, 1690, 1260, 1030, 725 cm^{-1}; mass spectrum (CI with isobutane), m/e 320 (M + 1); R_f 0.29 (ethyl acetate–hexanes, 1:2).

Aldol product 16e was formed from **12c** and *n*-butyraldehyde as a light yellow oil in 87% yield: ^1H NMR (300 MHz) δ 0.95 (t, 3 H, J = 7.5 Hz), 1.20–1.70 (m, 4 H), 2.65 (d, 1 H, J = 3 Hz), 3.50 (dd, 1 H, J = 12 Hz, J = 2.7 Hz), 3.65 (dd, 1 H, J = 12 Hz, J = 8 Hz), 3.82 (s, 3 H), 3.98 (m, 1 H), 5.66 (dd, 1 H, J = 8 Hz, J = 2.7 Hz), 6.17 (d, 1 H, J = 6.3 Hz), 7.20–7.60 (m, 5 H); IR (neat) 3440, 1755, 1705, 1215, 1045, 745, 690 cm^{-1}; mass spectrum (CI

Scheme V



with isobutane), m/e 400 (M + 1); R_f 0.16 (ethyl acetate–hexanes, 1:4).

Aldol product 17a was formed from **13** and benzaldehyde as an oil in 89% yield: ^{1}H NMR (300 MHz) δ 1.28 (d, 3 H), 2.98 (br, 1 H), 3.81 (s, 3 H), 4.45 (s, 1 H), 4.47 (d, 1 H), 4.98 (dd, 1 H), 5.07 (dq, 1 H, J = 6.6 Hz, J = 4.8 Hz), 5.11 (d, 1 H), 7.35 (m, 5 H); IR ($CHCl_3$) 3490, 3020, 1755, 1705 cm^{-1}; mass spectrum (CI with isobutane), m/e 324 (M + 1), 306 (M – H_2O + 1); R_f 0.48 (ethyl acetate–hexanes, 1:1). A small amount (<2%) of a slightly higher R_f material was isolated and determined to be the other erythro isomer by high-field ^{1}H NMR: ^{1}H NMR (300 MHz) δ 1.08 (d, 3 H), 3.10 (d, 1 H), 3.85 (s, 3 H), 4.57 (dd, 1 H), 4.77 (t, 1 H), 5.14 (dq, 1 H, J = 3.0 Hz, J = 6.9 Hz), 5.33 (dd, 1 H), 5.49 (m, 1 H), 7.32–7.55 (m, 5 H). Methanolysis of this product produced the corresponding methyl ester **24**, which was isographic with both authentic enantiomers **19** and **24** upon TLC and gas chromatographic analysis (retention time = 5.7 min with the GC programmed from 100 to 250 °C at 30°/min).

Aldol product 17b was formed from **13** and isobutyraldehyde as a colorless solid in 81% yield: mp 104–105 °C; ^{1}H NMR (300 MHz) δ 0.89 (d, 3 H), 1.01 (d, 3 H), 1.25 (d, 3 H), 1.70 (m, 1 H), 2.71 (d, 1 H), 3.60 (dd, 1 H), 3.80 (s, 3 H), 4.51 (dd, 1 H), 4.66 (t, 1 H), 4.88 (dq, 1 H, J = 6.9 Hz, J = 2.7 Hz), 5.18 (dd, 1 H); IR ($CHCl_3$) 3540, 2965, 1750, 1700 cm^{-1}; mass spectrum (CI with isobutane), m/e 290 (M + 1), 272 (M – H_2O + 1); R_f 0.41 (ethyl acetate–hexanes, 1:1). Anal. Calcd for $C_{12}H_{19}NO_5S$: C (49.81), H (6.62), N (4.84). Found: C (50.00), H (6.57), N (4.85).

Aldol product 18a was formed from **14** and benzaldehyde as an oil in 78% yield: ^{1}H NMR (300 MHz) δ 1.27 (d, 3 H), 3.00 (br, 1 H), 3.81 (s, 3 H), 4.45 (s, 1 H), 4.47 (d, 1 H), 4.97 (dd, 1 H), 5.06 (dq, 1 H, J = 6.3 Hz, J = 4.8 Hz), 5.10 (d, 1 H), 7.35 (m, 5 H); IR ($CDCl_3$) 3530, 2960, 1754, 1703 cm^{-1}; mass spectrum (CI with isobutane), m/e 324 (M + 1), 306 (M – H_2O + 1); R_f 0.48 (ethyl acetate–hexanes, 1:1).

Aldol product 18b was formed from **14** and isobutyraldehyde as a colorless solid in 83% yield: mp 104–105 °C; ^{1}H NMR (300 MHz) δ 0.93 (d, 3 H), 1.04 (d, 3 H), 1.28 (d, 3 H), 1.73 (m, 1 H), 2.69 (d, 1 H), 3.62 (m, 1 H), 3.83 (s, 3 H), 4.53 (dd, 1 H), 4.68 (t, 1 H), 4.91 (dq, 1 H, J = 3.0 Hz, J = 6.9 Hz), 5.20 (dd, 1 H); IR ($CDCl_3$) 3540, 2965, 1755, 1700 cm^{-1}; mass spectrum (CI with isobutane), m/e 290 (M + 1), 272 (M – H_2O + 1); R_f 0.41 (ethyl acetate–hexanes, 1:1). Anal. Calcd for $C_{12}H_{19}NO_5S$: C (49.81), H (6.62), N (4.84). Found: C (49.64), H (6.43), N (4.81).

General Procedure for the Methanolysis of Aldol Products. To a solution of 410 mg (1.21 mmol) of **16a** in 10 mL of methanol at 0 °C was added 500 mg (300 mol %) of finely powdered potassium carbonate. The cooling bath was removed, and the reaction mixture was stirred for 5 min. TLC analysis indicated the complete absence of **16a**. The reaction mixture was diluted with ether or ether–hexanes (1:1), and the suspension was filtered through a plug of Celite. The filtrate was concentrated under vacuum, and the residue was purified by column chromatography, or on the chromatotron, to provide the desired methyl ester **19** in 95% yield (223 mg) as a colorless oil: ^{1}H NMR (300 MHz) δ 1.13 (d, 3 H, J = 7.2 Hz), 2.79 (dq, 1 H, J = 4.0 Hz, J = 7.2 Hz), 2.95 (d, 1 H, J = 3 Hz), 3.68 (s, 3 H), 5.11 (dd, 1 H, J = 4.0 Hz, J = 3 Hz), 7.33 (m, 5 H); IR (neat) 3460, 1710, 1190, 1025, 690 cm^{-1}; mass spectrum, m/e 194 (M$^+$); R_f 0.39 (ethyl acetate–hexanes, 1:3); $[\alpha]_D$ +22.6° (c 0.76, $CHCl_3$) [lit.[1] $[\alpha]_D$ +23.2° (c 3.2, $CHCl_3$)]. This rotation corresponds to >97% ee. However, we have found that comparison of optical rotation values can be very misleading and prefer using high field chiral NMR shift studies to confirm the % ee. Thus, several of the values for the % ee in the following examples will have been either confirmed or determined solely by the use of chiral shift studies. These studies include controls in which solutions of one enantiomer were intentionally spiked with varying amounts of the opposite enantiomer to determine the NMR detection limits. In all cases, less than 1% the opposite enantiomer could be clearly detected by observing the induced shifts of the methyl singlets of the esters.

Compound **19** was also obtained from methanolysis of **17a** in 67% yield and in 98% ee as determined by chiral NMR shift studies. The opposite optical isomer, **24**, was also prepared in 73% yield (98% ee) by methanolysis of **18a**.

Methyl ester 20 was prepared by the methanolysis of **16b** in 92% yield as a colorless oil: ^{1}H NMR (300 MHz) δ 0.88 (d, 3 H, J = 6.6 Hz), 1.00 (d, 3 H, J = 6.6 Hz), 1.18 (d, 3 H, J = 7.2 Hz), 1.67 (m, 1 H), 2.57 (d, 1 H, J = 4.2 Hz), 2.68 (dq, 1 H, J = 3.6 Hz, J = 7.2 Hz), 3.57 (ddd, 1 H, J = 7.2 Hz, J = 4.2 Hz, J = 3.6 Hz), 3.70 (s, 3 H); IR (neat) 3490, 2690, 1725 cm^{-1}; mass spectrum, m/e 160 (M$^+$); $[\alpha]_D$ +7.5° (c 1.30, $CHCl_3$), 97% ee [lit.[1] $[\alpha]_D$ +7.7° (c 5.4, $CHCl_3$)].

Compound **20** was also obtained from the methanolysis of **17b** in 60% yield and in 98% ee as determined by chiral NMR shift studies. The opposite optical isomer, **25**, was also prepared in 58% yield (99% ee) by methanolysis of **18b**.

Methyl ester 21 was prepared by the methanolysis of **16c** in 85% yield as a colorless oil: ^{1}H NMR (300 MHz) δ 0.87 (t, 3 H, J = 7.5 Hz), 1.70 (m, 2 H), 2.65 (dt, 1 H, J = 5.4 Hz, J = 6 Hz), 2.85 (d, 1 H, J = 3 Hz), 3.60 (s, 3 H), 4.94 (dd, 1 H, J = 5.4 Hz, J = 3 Hz), 7.20–7.40 (m, 5 H); IR (neat) 3480, 1730, 1170, 1030, 700 cm^{-1}; mass spectrum, m/e 208 (M$^+$); $[\alpha]_D$ +12° (c 1.58, $CHCl_3$). A chiral NMR shift study with 0.2 equiv of Eu(hfc)$_3$ clearly distinguished the two enantiomers of **21** (especially the methyl ester singlets) and indicated that **21** was formed in at least 96% ee. The validity of the chiral shift study was confirmed by preparing racemic **21** by using a nonchiral thiazolidinethione[8] and repeating the chiral shift study.

Methyl ester 22 was prepared by the methanolysis of **16d** in 85% yield as a colorless liquid: ^{1}H NMR (300 MHz) δ 0.90–1.15 (m, 9 H), 1.60–1.80 (m, 3 H), 2.91 (d, 1 H, J = 4.2 Hz), 2.50 (dt, 1 H, J = 5.4 Hz, J = 9 Hz), 3.51 (m, 1 H), 3.71 (s, 3 H); IR (neat) 3500, 1730, 1200, 1170, 995 cm^{-1}; mass spectrum, m/e 156 (M$^+$ – H_2O); $[\alpha]_D$ +7.6° (c 3.07, $CHCl_3$). A chiral NMR shift study indicated that **22** was formed in at least 99% ee.

Methyl ester 23 was prepared by the methanolysis of **16e** in 82% yield as a colorless oil. The crude **23** [^{1}H NMR (300 MHz) δ 0.95 (t, 3 H, J = 7.5 Hz), 1.25–1.65 (m, 4 H), 3.02 (d, 1 H, J = 3 Hz), 3.61 (d, 1 H, J = 6 Hz), 3.71 (s, 3 H), 3.96 (m, 1 H), 7.30–7.45 (m, 5 H); IR (neat) 3440, 1730, 1430, 1255, 1010, 730, 680 cm^{-1}; mass spectrum, m/e 254 (M$^+$)] was converted to the corresponding desulfurized carboxylic acid **26**. Thus, to a refluxing solution of **23** (280 mg, 1.1 mmol) and tri-n-butyltin hydride (400 μL, 1.50 mmol) in toluene (8 mL) under nitrogen was added AIBN (5 mg). Refluxing was continued for another 15 min, at which time TLC analysis indicated the total disappearance of **23**. Carbon tetrachloride (5 mL) was added, and the mixture was heated for an additional 5 min. The reaction mixture was cooled and concentrated under reduced pressure, and the resulting colorless oil was chromatographed on silica gel (ethyl acetate–hexanes, 1:5) to provide the methyl ester of **26** [^{1}H NMR (90 MHz) δ 0.7–1.10 (br t, 3 H), 1.20–1.60 (br, 4 H), 2.45 (d, 1 H, J = 3.5 Hz), 2.50 (s, 1 H), 2.90 (d, 1 H, J = 3 Hz), 3.75 (s, 3 H), 4.05 (m, 1 H); IR (neat) 3450, 1720 cm^{-1}; mass spectrum, m/e 146 (M$^+$); R_f 0.52 (ethyl acetate–hexanes, 1:3)]. This ester was saponified to provide acid **26** in the following manner. The ester (100 mg, 0.684 mmol) was dissolved in 5 mL of methanol, and 1 mL of 2 N NaOH was added. The resulting mixture was stirred at room temperature overnight and then evaporated under reduced pressure to a solid residue. The residue was triturated with CH_2Cl_2 (50 mL) and then decanted to remove non-ionic material. Then 3 N HCl was added to the residue until the solution was at pH 2. The acidic aqueous solution was extracted with three portions of ethyl acetate. The ethyl acetate extracts were combined, dried over $MgSO_4$, filtered, and evaporated to provide **26** as an oil in 97% yield: ^{1}H NMR (90 MHz) δ 0.8–1.10 (br t, 3 H), 1.20–1.80 (br, 4 H), 2.50 (d, 1 H, J = 3.5 Hz), 2.60 (s, 1 H), 4.15 (m, 1 H), 7.10 (br, 2 H); IR (neat)

2400-3600 (br), 1710, 1220 cm^{-1}; mass spectrum, m/e 132 (M^+); $[\alpha]_D$ +27° (c 1.2, $CHCl_3$) [lit.[1] (for the optical antipode) $[\alpha]_D$ -27.2° (c 2.1, $CHCl_3$)].

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The Synthesis of Indolizines: The Reaction of α-Halo Pyridinium Salts with β-Dicarbonyl Species

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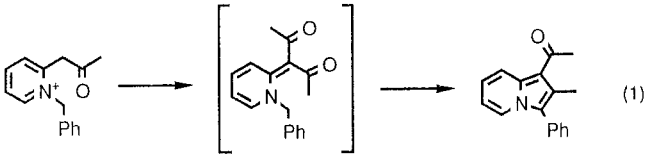
The reaction of β-keto esters and β-diketones with readily accessible 2-halo pyridinium salts in the presence of DBU serves as a rapid and convenient method for the synthesis of substituted indolizines. The use of diethyl malonate as the dicarbonyl component of the reaction enables the preparation of previously undescribed 2-hydroxyindolizines.

In the course of synthetic efforts toward the design of antiinflammatory agents, it became necessary to prepare a series of 1-carboxylic acid ester indolizines for testing. Generally, indolizines have been prepared by the reaction of pyridine salts with carboxylic acid derivatives and cyclization of the resulting quaternary salt with mild base.[1] While these methods are useful for preparing many indolizine derivatives, they are inconvenient for synthesizing indolizines that possess an ester residue at the 1-position, since the pyridine starting material is either expensive or difficult to synthesize.[2] An alternative route that utilizes acetylenes and simpler pyridinium salts is limited by the availability of the acetylenes and the constraints of their pericyclic reaction.[3]

The indolizine synthesis that has been attributed to Scholtz has been shown by Kröhnke and others to utilize the anhydro base 1 as an intermediate (eq 1).[4] Similar



(1)

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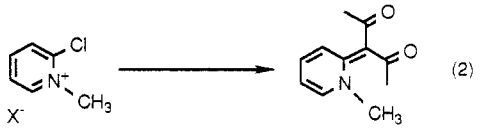
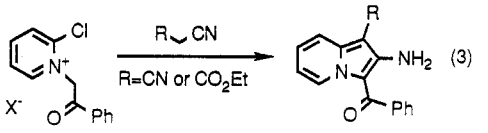
anhydro bases have been synthesized as a result of the reaction of α-halopyridinium salts with β-dicarbonyl compounds in the company of base (eq 2).[5] Although there are many examples of failure to cyclize these compounds



(2)

to indolizines, Kröhnke demonstrated that the reaction between α-chloropyridinium ylides and either malononitrile or ethyl cyanoacetate in the presence of Hunig's base (diisopropylethylamine) yielded 2-aminoindolizines **2** (eq 3).[6] We sought to broaden the scope of this reaction and utilize it in a general synthesis of indolizines.



(3)

2

Results

Halopyridinium salts **3** were prepared from 2-bromo(or 2-chloro)pyridine and an appropriate α-halo ketone or ester by heating them neat at 120 °C for 1 hour and then continuing the reaction at 80 °C for 22 h or diluting the mixture with toluene and heating at reflux for 16 h. The resulting solid was collected by filtration and recrystallized from EtOH.

Following the procedure published by Kröhnke, ethyl acetoacetate and 2-bromo 1-(2-oxopropyl)pyridinium chloride (**3**, $R_3 = CH_3$) were stirred together in *n*-propanol with $(i\text{-Pr})_2NEt$ (Hunig's base) for 24 h, but only a faint trace of nonpolar product was visible by TLC. After examining several parameters it was found that the reaction, when run in CH_3CN with DBU as base, yielded an indolizine in 44% recrystallized yield (Table I, entry 1). Further, these conditions could be applied with equal success to several other β-keto esters and pyridinium salts (Table I, entries 2-11). When the isopropyl β-keto ester **4** (R_1 = OEt, R_2 = *i*-Pr) was employed, we unexpectedly isolated the corresponding carboxylic acid in good yield (entry 5). This hydrolysis was not observed with any of the other keto esters utilized.

We examined the consequences of changing bases and solvents in the reaction; the results are displayed in Table II. Numerous organic (Et_3N, Hunig's base, DaBCO, and pyridine) and inorganic (K_2CO_3, NaOH, and NaOMe)

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