HETEROCYCLES, Vol. 58, 2002, pp. 251-258, Received, 4th March, 2002

IMINO ENE REACTIONS OF ENANTIOPURE *N*-SULFINYLIMINO ESTERS: ASYMMETRIC SYNTHESIS OF 1-OXO-1 λ^4-ISOTHIAZOLIDINE-3-CARBOXYLATES‡

Franklin A. Davis,* Junya Qu, Vaidyanathan Srirajan, Reni Joseph, and Donald D. Titus

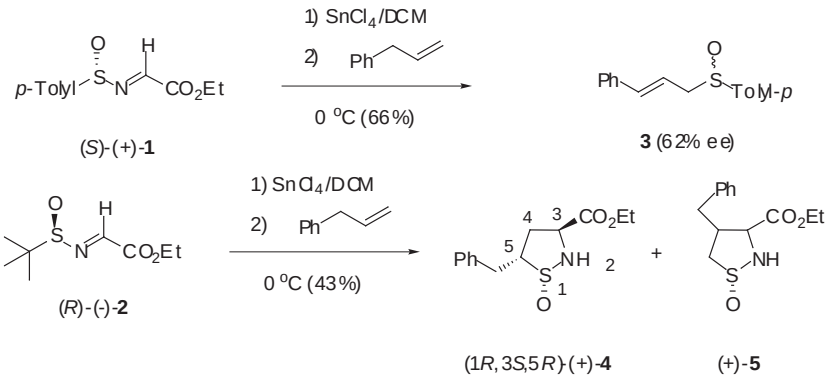
Department of Chemistry, Temple University, Philadelphia, PA 19122, U.S.A.

fdavis@temple.edu

Abstract – The imino ene reaction of (*R*)-(-)-*N*-(*tert*-butanesulfinyl)iminoacetate (**2**), allyl benzene and $SnCl_4$ results in a novel rearrangement affording 1-oxide isothiazolidine-3-carboxylate (**4**) as the major product. The structure of **4** was established by X-Ray crystallography and conversion into α-amino acids that were prepared independently using the sulfinimine-mediated asymmetric Strecker synthesis.

Glyoxylate imines provide access to nonproteinogenic α-amino acid derivatives through cycloaddition reactions,[1,2] radical addition,[3] nucleophilic addition,[4-7] or ene reactions.[8] The imino ene reaction is particularly attractive because it provides access to γ,δ-unsaturated α-amino acids that are valuable building blocks for organic syntheses.[9] The diastereoselective imino ene reaction has been extensively explored by Weinreb[10] and others[11] and an enantioselective catalytic version employing an *N*-tosyl glyoxylate imino ester has been reported by Lectka.[12] Recently we described the synthesis of enantiopure *N*-sulfinyl imino esters ((*S*)-(+)- **1**) and ((*R*)-(-)-**2**) from the condensation of the corresponding chiral sulfinamides ($RS(O)NH_2$)

Scheme 1



‡Dedicated to Professor Albert I. Meyers on the occasion of his 70th birthday and in recognition of his pioneering contributions to the art of asymmetric synthesis.

with ethyl glyoxylate.[13] The Lewis acid catalyzed addition of organometallic reagents to ethyl (*R*)-(-)-*N*-(*tert*-butanesulfinyl)iminoacetate (**2**) resulted in a highly efficient asymmetric synthesis of α-amino acids. In this paper we describe preliminary studies of the Lewis acid catalyzed imino ene reaction of **1** and **2** and the discovery of a novel ring-forming reaction.

Reaction of iminoacetate ((*S*)-(+)-**1**) with 2.0 equiv of $SnCl_4$ or Et_2AlCl at room temperature followed by addition of 2 equivalents of allylbenzene afforded 65-67% yield of *E*-(+)-3-(*p*-toluenesulfinyl)-1-phenyl-1-propene (**3**) based on the $J_{1,2}$ coupling constant of 15.0 Hz (Scheme 1). A chiral shift reagent experiment with $Eu(hfc)_3$ indicates that the ee was 62%. Since attack of the alkene is apparently favored at the sulfinyl group in **1**, we next explored the ene reaction with (*R*)-(-)-**2**, which has the bulky *tert*-butyl sulfinyl group. Lewis acids such as $BF_3{\cdot}OEt_2$, $ZnCl_2$, $Ti(OEt)_4$, and $Yb(O_3SCF_3)$ failed to give any reaction with allylbenzene, and Me_3Al or Me_2AlCl resulted in decomposition. However, with 2.0 equiv of $SnCl_4$ in DCM at 0 °C followed by addition of 1.0 equiv of allylbenzene unexpectedly resulted in a 43% isolated yield, following preparative TLC, of 5- and 4-benzyl-1-oxide-isothiazolidine-3-carboxylates (**4**) and (**5**) as a 1.5:1 mixture of products (Scheme 1). The structures of **4** and **5** are supported by the absences in the ^1H NMR of protons characteristic of olefinic and *tert*-butyl groups and the presence of benzyl protons at δ 2.9-3.3 ppm. The IR spectrum exhibits absorptions at 3500-3300 cm^{-1} (NH) and at 1082 cm^{-1} (SO). To date all attempts to improve the yield and/or ratio of **4** and **5** by varying reaction conditions have proved unsuccessful.

The relative stereochemistry of the major isomer ((+)-**4**) was determined by X-Ray crystallography and is shown in Figure 1. To establish the absolute stereochemistry of **4** the sulfoxide moiety was removed, which afforded an α-amino acid whose structure would be determined by independent asymmetric synthesis. Oxidation of (+)-**4** with *m*-CPBA gave the sulfonamide ((+)-**6**) in 92% yield (Scheme 2). γ-Sultams such as **6** are analogs of pyroglutamic acid and have been used in the development of peptide inhibitors and to generate abzymes.[14] Surprisingly, desulfurization of **6** with Raney Ni resulted in two α-amino acids ((*S*)-(+)-**7**) and ((*S*)-(-)-**8**) that differed only in the number of *N*-ethyl groups and were isolated by preparative TLC in 28 and 12% yield, respectively. Reductive amination caused by acetaldehyde in the ethanol is the likely cause for the formation of these products.

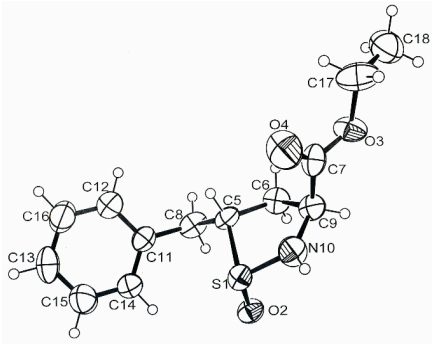
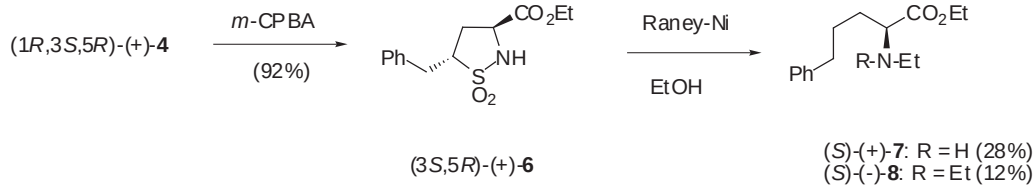


Figure 1: ORTEP view of (+)-**4**.

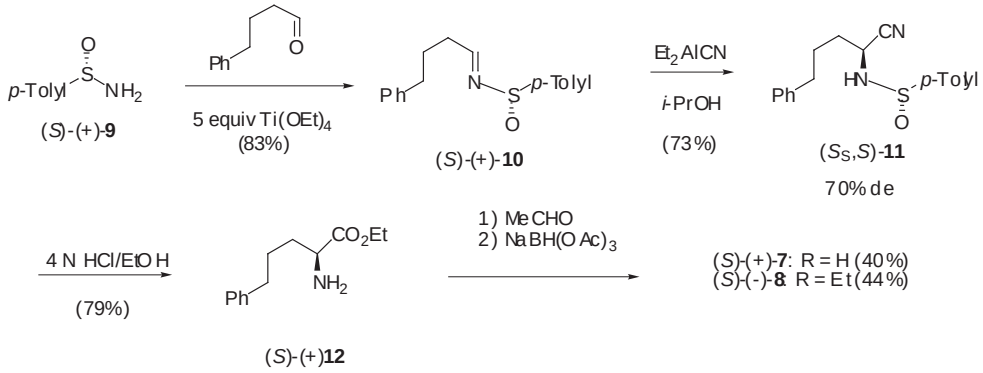
The absolute configurations of amino acids (**7**) and (**8**) were established by independent synthesis using the sulfinimine-mediated asymmetric Strecker synthesis (Scheme 3).[15] 4-Phenylbutyraldehyde was condensed with commercially available (*S*)-(+)-*p*-toluenesulfinamide (**9**) and $Ti(OEt)_4$ to give sulfinimine ((*S*)-(+)-**10**) in 83% yield.[16] Next, the sulfinimine was treated with ethylaluminum cyanoisopropoxide [EtAl(O-*i*-Pr)CN], generated *in situ* by addition of 1.0 equiv of *i*-PrOH to 1.5 equiv. of diethylaluminum cyanide (Et_2AlCN), to give the amino nitrile (**11**) in 73% yield and 70% de. Since the sulfinyl group controls the stereoselectivity *Re* face addition of CN affords (S_S,*S*)-(+)-**11** as the major diastereoisomer.[15] The diastereomeric amino

Scheme 2



nitriles were separated by flash chromatography and treated with 4 N HCl-EtOH. This treatment not only removes the sulfinyl group, but hydrolyzes the nitrile to give the α-amino acid ((*S*)-(+)-**12**) in 79% yield. The hydrochloride salt of (+)-**12** was reacted with acetaldehyde followed by reduction with sodium triacetoxyborohydride to give (+)-**7** and (-)-**8** in 40 and 44% yield. This result establishes that the amino esters have the *S*-configuration, and by extension isothiazolidine ((+)-**4**) has the (1*R*,3*S*,5*R*)- configuration.

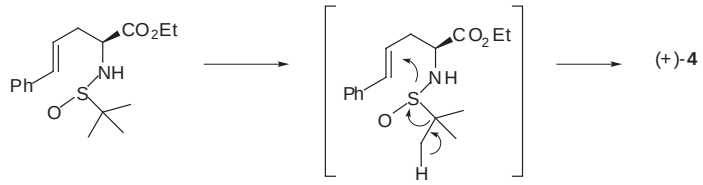
Scheme 3



We tentatively assign the structure of the other isomer to (+)-**5** based on COSEY, NOESY, and HETCOR experiments. The ^{13}C NMR chemical shift of C-5, adjacent to the sulfinyl groups, appears in **4** and **5** at 66 and 59 ppm respectively, and that of C-4 at 34 and 45 ppm, respectively. Furthermore, an NOE was noted between proton C-3 and the benzyl protons in **5**, but was absent in **4**.

The mechanism for formation of **4** and **5** is unknown. We speculate, however, that **4** could result from a rearrangement of β,γ-unsaturated α-amino acid (**13**), which may be formed in an imino ene reaction (Scheme 4). Indeed this amino acid was detected in the ^{1}H NMR of the crude reaction mixture (δ 6.6, 6.4 ppm), but could not be isolated. Activation of the olefinic double bond in **13** by $SnCl_4$,[17] followed by attack of the sulfinyl sulfur at C-3 of the alkene (i.e., **14**) would furnish the product. The driving force for this novel ring-forming reaction is the expulsion of a molecule of isobutylene. Other mechanistic schemes cannot at this time be ruled out.

Scheme 4



13 **14**

ACKNOWLEDGMENT

We thank Professor David Dalton, Temple University, for stimulating discussions. This work was supported by grants from the National Institutes of Health (GM57870) and the National Science Foundation.

EXPERIMENTAL

General procedure. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). Analytical and preparative thin-layer chromatography was performed on precoated silica gel plates (250 and 1000 microns) purchased from Analtech Inc. TLC plates were visualized with UV in an iodine chamber. THF was freshly distilled under argon from a purple solution of sodium and benzophenone. Dichloromethane was distilled over calcium hydride under argon.

Ethyl (*S*)-(+)-*N*-(*p*-toluenesulfinyl)iminoacetate (**1**),[13] ethyl (*R*)-(-)-*N*-(*tert*-butanesulfinyl)iminoacetate (**2**),[13] and (*S*)-(+)-*p*-toluenesulfinamide (**9**)[16] were prepared as previously described.[13] 4-Phenyl-1-butyraldehyde was prepared by Swern oxidation of 4-phenyl-1-butanol.[18] Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

(+)-(*E*-3-Phenylprop-2-ene)-*p*-toluenesulfoxide (3). In a 25-mL single-neck, round-bottom flask equipped with a magnetic stir bar and argon-filled balloon was placed (*S*)-(+)-*N*-(*p*-toluenesulfinyl)iminoacetate (**1**) (0.058 g, 0.24 mmol) in CH_2Cl_2 (5 mL) at 0 ^{0}C. To the reaction mixture was added $SnCl_4$ (0.0572 mL, 0.49 mmol) and allylbenzene (0.072 mL, 0.54 mmol). The reaction, monitored by TLC (EtOAc-pentane 1:1), was completed in 3 h and quenched with H_2O (2 mL). The solution was washed with CH_2Cl_2 (2 × 5 mL), the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude sulfoxide was purified by preparative TLC (EtOAc-pentane 1:1) to afford 0.041 g (66%) of a solid; mp 96°C; $[\alpha]_D^{20}$ +10.2^o (*c* 0.20, $CHCl_3$); IR (KBr) 1703, 1605, 1495, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 3.68 (d, *J* = 6.4 Hz, 2H), 6.00 (m, 1H), 6.45 (d, *J* = 15.0 Hz, 1H), 7.20~7.40 (m, 7H), 7.52 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 22.1, 61.5, 116.9, 125.1, 127.2, 128.8, 129.3, 130.4, 136.8, 139.0, 140.4, 142.3. HRMS calcd for $C_{16}H_{16}OS$ (M+Na) 279.0810. Found (M+Na) 279.0820.

(1*R*,3*S*,5*R*)-(+)-5-Benzyl-1-oxo-1λ^4-isothiazolidine-3-carboxylic acid ethyl ester (4) and (+)-4-benzyl-1-oxo-1λ^4-isothiazolidine-3-carboxylic acid ethyl ester (5). In a 50-mL, single-neck, round-bottom flask equipped with a magnetic stir bar and argon filled balloon was placed (-)-**2** (0.069 g, 0.34 mmol) in CH_2Cl_2 (3 mL). The solution was cooled to 0 ^{0}C, $SnCl_4$ (0.067 mL, 0.57 mmol)

and allylbenzene (0.090 mL, 0.68 mmol) were added. The reaction mixture was warmed to rt, monitored by TLC for completion (2.5 h), and quenched by addition of sat. NH_4Cl solution (2 mL). The solution was washed with CH_2Cl_2 (2 × 10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated. Purification by preparative TLC (EtOAc-pentane 1:1) gave 0.024 g (26%) (+)-**4** as a white solid and 0.016 g (17%) (+)-**5** as a colorless liquid. (+)-**4**: mp 97 °C; $[\alpha]^{20}_D$ +5.3° (*c* 1.0, $CHCl_3$); IR (KBr) 3292, 2932, 1721, 1179, 1082 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, *J*= 7.0 Hz, 3H), 2.51 (m, 1H), 2.60 (m, 1H); 2.91 (m, 1H), 3.18 (m, 2H), 4.19 (m, 2H), 4.54 (m, 1H), 4.92 (s, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.8, 31.8, 34.0, 61.9, 62.6, 66.5, 127.5, 129.5, 129.6, 139.0, 172.7. HRMS calcd for $C_{13}H_{17}NO_3S$ (M+H) 268.1007. Found (M+H) 268.1003.

(+)-**5**: $[\alpha]^{20}_D$ +2.6° (*c* 1.0, $CHCl_3$); IR (NaCl) 3235, 2980, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, *J* 7.0 Hz, 3H), 2.83 (m, 1H), 3.03 (m, 2H); 3.12 (m, 1H), 3.31 (m, 1H), 4.21 (q, *J* 6.6 Hz, 2H), 4.54 (m, 1H), 4.89 (s, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.8, 41.2, 45.0, 59.4, 62.7, 67.7, 127.3, 129.4, 129.8, 139.6, 172.2. HRMS calcd for $C_{13}H_{17}NO_3S$ (M+H) 268.1007. Found (M+H) 268.0999.

(3*S*,5*R*)-(+)-5-Benzyl-1,1-dioxo-1λ⁶-isothiazolidine-3-carboxylic acid ethyl ester (6). In a 50-mL, single-neck, round-bottom flask equipped with a magnetic stir bar and argon filled balloon was placed (+)-**4** (0.039 g, 0.15 mmol) in CH_2Cl_2 (5 mL). *m*-Chloroperbenzoic acid (70%) (0.12 g, 0.49 mmol) was added, and the solution was stirred at rt for 4.5 h. The reaction mixture was washed with sodium thiosulfate solution (5 mL), sat. sodium bicarbonate (5 mL), dried ($MgSO_4$), and concentrated. Filtration through a short column of silica gel afforded 0.038 g (92%) (+)-**6;** mp 93°C; $[\alpha]^{20}_D$ +4.3° (*c* 1.5, $CHCl_3$); IR (KBr) 3279, 2984, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.3 Hz, 3H), 2.53 (m, 2H), 2.87 (dd, *J* = 9.2, 14.0 Hz, 1H); 3.21 (m, 1H), 3.35 (dd, *J* = 5.5, 14.0 Hz, 1H), 4.10 (m, 1H), 4.27 (m, 2H), 5.06 (d, *J* = 3.3 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.8, 31.8, 34.0, 61.9, 62.6, 66.5, 127.5, 129.5, 129.6, 139.0, 172.7. HRMS calcd for $C_{13}H_{17}NO_4S$ (M+H) 284.0943. Found (M+H) 284.0948.

(*S*)-(+)-4-Phenylbutylidene-*p*-toluenesulfinamide (10). In a 100-mL single-neck round-bottom flask equipped with a magnetic stir bar and argon-filled balloon was placed (*S*)-(+)-*p*-toluenesulfinamide (**9**) (1.10 g, 7.1 mmol) and 4-phenyl-1-butyraldehyde (0.80 g, 5.5 mmol) in CH_2Cl_2 (20 mL). Titanium (IV) ethoxide (6.3 mL, 30.0 mmol) was added and the reaction mixture was stirred for 8 h at rt. At this time the solution was cooled to 0 °C, H_2O (40 mL) was added and the solution was filtered through Celite. The Celite was washed with CH_2Cl_2 (40 mL), the phases were separated, and the organic phase was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc: hexane, 15:85) afforded 1.30 g (83%) of (+)-**10** as a colorless oil; $[\alpha]^{20}_D$ +241° (*c* 1.3, $CHCl_3$); IR (NaCl) 3026, 2924, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (m, 2H), 2.40 (s, 3H), 2.50 (m, 2 H), 2.65 (t, *J* = 7.3 Hz, 2H), 7.13~7.40 (m, 7H), 7.56 (d, *J* = 8.1 Hz, 2H), 8.24 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 27.3, 35.5, 35.6, 124.9, 126.4, 128.8, 128.9, 130.2, 141.7, 142.1, 142.2, 167.1. HRMS calcd for $C_{17}H_{19}NOS$ (M+H) 286.579. Found (M+H) 286.571.

(2*S*)-(+)-[*N*-(*S*)-*p*-Toluenesulfinyl]-2-amino-5-phenylpentanenitrile (11). In a 100-mL single-neck round-bottom flask equipped with a magnetic stir bar and argon-filled balloon was placed (+)-**10** (0.30 g, 1.1 mmol) in THF (10 mL) and cooled to –78 °C. In a separate 25-mL single-neck round-

bottom flask equipped with a magnetic stir bar and a argon-filled balloon was added a solution of diethylaluminium cyanide (1.6 mL, 1.6 mol) in THF (10 mL) and the solution was cooled to -78°C. To the solution was added *i*-PrOH (0.081 mL, 1.1 mmol), the reaction mixture was brought to rt, stirred for 30 min, and cannulated to the solution of (+)-**10** at –78 °C. After the reaction mixture was slowly brought to rt, and stirred for 10 h, it was cooled to –78 °C and quenched with sat. NH_4Cl solution (5 mL). The suspension was filtered through Celite, extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc:hexane: $CHCl_3$, 20:50:30) afforded 0.24 g (73%) of (+)-**11** as a white solid; mp 86°C; $[\alpha]^{20}_D$ +52.5° (*c* 1.0, $CHCl_3$); IR (KBr) 3222, 3024, 2956, 2241 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80~1.88 (m, 4H), 2.43 (s, 3H), 2.65 (t, *J* = 7.3 Hz, 2H), 4.08 (dd, *J* = 7.0, 14.0 Hz, 1H), 4.41 (d, *J* = 7.3 Hz, 1H), 7.15~7.40 (m, 7H), 7.59 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 22.1, 27.6, 35.4, 35.5, 42.3, 119.3, 126.6, 126.9, 129.1, 129.2, 130.7, 140.0, 141.4, 143.1; HRMS calcd for $C_{18}H_{20}N_2OS$ (M+Na) 335.1194. Found (M+Na) 335.1198.

(*S*)-(+)-2-Amino-5-phenylpentanoic acid ethyl ester (12). In a 100-mL, single-neck, round-bottom flask equipped with a magnetic stir bar and a water condenser was placed (+)-**11** (0.21 g, 0.7 mmol) in 4.0 N HCl- EtOH (20 mL). The solution was refluxed for 5 h, cooled to rt, concentrated, H_2O (10 mL) added, and neutralized with ammonium hydroxide. The reaction mixture was extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc: hexane, 70:30) afforded 0.12 g (79%) of (+)-**12** as a colorless oil; $[\alpha]_D^{20}$ +14.5° (*c* 2.0, $CHCl_3$);); IR (NaCl) 3336, 3276, 2986, 1710, 1129 cm^{-1}; ^1H NMR ($CDCl_3$) 1.26 (t, *J* = 6.9 Hz, 3H), 1.54~1.75 (m, 4H), 2.65 (m, 2H), 3.43 (dd, *J* = 5.1, 7.3 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 7.17~7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.9, 28.1, 35.2, 36.2, 55.1, 61.4, 126.5, 129.0, 129.1, 142.6, 176.7. HRMS calcd for $C_{13}H_{19}NO_2$ (M+H) 222.1494. Found (M+H) 222.1494.

(*S*)-(+)-2-Ethylamino-5-phenylpentanoic acid ethyl ester (7) and (*S*)-(-)-2-diethylamino-5-phenylpentanoic acid ethyl ester (8). In a 50-mL, single-neck, round-bottom flask equipped with a magnetic stir bar and water condenser was placed (+)-**6** (0.028 g, 0.1 mmol) in EtOH (5 mL). To this solution was added Raney nickel (*ca*. 1.0 g) and the reaction mixture was heated and refluxed for 7 h. At this time the solution was filtered, concentrated, and purified by preparative TLC (EtOAc: hexane, 1: 1) to afford (+)-**7** (0.007 g, 28%) and (-)-**8** (0.004 g, 12%) as colorless oils.

(*S*)-(+)-**7**: $[\alpha]^{20}_D$ +6.8° (*c* 0.5, $CHCl_3$); IR (NaCl) 3321, 2932, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.67 (m, 4H), 2.48 (m, 1H), 2.62 (m, 3H), 3.24 (t, *J* = 6.2 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 7.13~7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.0, 16.0, 28.1, 33.9, 36.3, 43.1, 61.1, 62.0, 126.4, 129.0, 129.1, 142.7, 176.3; HRMS calcd for $C_{15}H_{23}NO_2$ (M+H) 250.1807. Found (M+H) 250.1808.

(*S*)-(-)-**8**: $[\alpha]^{20}_D$ –2.7° (*c* 1.3, $CHCl_3$); IR (NaCl) 2968, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.0 Hz,6H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.63~2.73 (m, 4H), 2.45 (m, 2H), 2.61~2.73 (m, 4H), 3.35 (t, *J* = 6.9 Hz, 1H), 4.13 (m, 2H), 7.13~7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.0, 16.0, 28.1, 33.9, 36.3, 43.1,

61.1, 62.0, 126.4, 129.0, 129.1, 142.7, 176.3. HRMS calcd for $C_{17}H_{27}NO_2$ (M+H) 278.2120. Found (M+H) 278.2119.

From amino acid ((*S*)-(+)-12). In a 50-mL single-neck, round-bottom flask equipped with a magnetic stir bar and an argon-filled balloon was placed the HCl salt of (+)-**12** (0.038 g, 0.17 mmol) in dichloroethane (6 mL), followed by acetaldehyde (*ca*. 0.08 mL, 2.3 mmol). The solution was stirred for 15 min at rt and acetic acid (0.012 mL, 0.21 mmol) and sodium triacetoxyborohydride (0.053 g, 0.25 mmol) were added. After 25 min the reaction mixture was quenched with sat. NH_4Cl solution (3 mL), the solution was extracted with DCM (2 × 10 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Purification by preparative TLC (EtOAc:hexane, 1:1) afforded (+)-**7** (0.017 g, 40%) and (-)-**8** (0.021 g, 44%) as colorless oils. Their properties were identical to the materials prepared from (+)-**6**.

REFERENCES

1. For Diels-Alder reactions see: a) T. Hamada, T. Zenkoh, H. Sato, and O. Yonemitsu, *Tetrahedron Lett*., 1991, **32**, 1649. b) P. Hamley, A. B. Holmes, A. Kee, T. Ladduwahetty, and D. F. Smith, *Synlett*, 1991, 29. c) P. Hamley, G. Helmchen, A. B. Holmes, D. R. Marshall, J. W. M. MacKinnon, D. F. Smith, and J. W. Ziller, *J. Chem. Soc., Chem. Commun.*, 1992, 786. d) P. D. Bailey, D. J. Londesbrough, T. C. Hancox, J. D. Heffernan, and A. B. Holmes, *J. Chem. Soc., Chem. Commun.*, 1994, 2543. e) A. B. Holmes, A. Kee, T. Ladduwahetty, and D. F. Smith, *J. Chem. Soc., Chem. Commun.*, 1990, 1412. f) H. Abraham and L. Stella, *Tetrahedron*, 1992, **48**, 9707. g) M. Maggini, M. Prato, and G. Scorrano, *Tetrahedron Lett.*, 1990, **43**, 6243. h) G. R. Heintzelman and S. M. Weinreb, *J. Org. Chem.*, 1996, **61**, 4594. i) S. Yao, M. Johannsen, R. G. Hazell, and K. A. Jørgensen, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 3121.
2. For an example of a [2+2] cycloaddition see M. Barreau, A. Commercon, S. Mignani, D. Mouysset, P. Perfetti, and L. Stella, *Tetrahedron*, 1998, **54**, 11501.
3. M. P. Bertrand, L. Feray, R. Nouguier, and L. Stella, *Synlett*, 1998, 780.
4. Organometallic additions: a) J.-C. Fiaud and H. B. Kagan, *Tetrahedron Lett.*, 1970, 1813. b) J.-C. Fiaud, and H. B. Kagan, *Tetrahedron Lett.*, 1971, 1019. c) P. Münster and W. Steglich, *Synthesis*, 1987, 223. d) L. M. Harwood, K. J. Vines, and M. G. B Drew, *Synlett*, 1996, 1051. e) G. Courtois, and L. Miginiac, *J. Organomet. Chem.*, 1989, **376**, 235. f) G. Courtois and L. Miginiac, *J. Organomet. Chem.*, 1993, **450**, 33. g) G. Courtois and L. Miginiac, *J. Organomet. Chem.*, 1993, **452**, 5. h) H. Uno, S. Okada, T. Ono, Y. Shiraishi, and H. Suzuki, *J. Org. Chem.*, 1992, **57**, 1504. i) Y. Yamamoto and W. Ito, *Tetrahedron*, 1988, **44**, 5415. j) P. Bravo, M. Crucianelli, B. Vergani, and M. Zanda, *Tetrahedron Lett.*, 1998, **39**, 7771.
5. Boron reagents: a) Y. Yamamoto, W. Ito, and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1985, 1131. b) Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu, and W. Ito, *J. Am. Chem. Soc.*, 1986, **108**, 7778.

6. Allylstannanes: a) D. J. Hallet and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1995, 657. b) D. J. Hallet and E. J. Thomas, *Tetrahedron: Asymmetry*, 1995, **6**, 2575. c) G. W. Bradley, D. J. Hallet, and E. J. Thomas, *Tetrahedron: Asymmetry*, 1995, **6**, 2579. d) C. Bellucci, P. G. Cozzi, and A. Umani-Ronchi, *Tetrahedron Lett.*, 1995, **36**, 7289.

7. Carbon nucleophiles: a) E. Hagiwara, A. Fujii, and M. Sodeoka, *J. Am. Chem. Soc.*, 1998, **120**, 2474. b) D. Ferraris, B. Young, T. Dudding, and T. Lectka, *J. Am. Chem. Soc.*, 1998, **120**, 4548. c) D. Ferraris, B. Young, C. Cox, W. J. Drury III, T. Dudding, and T. Lectka, *J. Org. Chem.*, 1998, **63**, 6090. d) D. P. G. Hamon, R. A. Massy-Westropp, and P. Razzino, *Tetrahedron*, 1992, **48**, 5163. e) Y. Yamamoto, Y. Kubota, Y. Honda, H. Fukui, N. Asao, and H. Nemoto, *J. Am. Chem. Soc.*, 1994, **116**, 3161.

8. For reviews on the imino ene reaction see a) R. M. Borzilleri and S. M. Weinreb, *Synthesis*, 1995, 347. b) S. M. Weinreb, *Topics in Current Chemistry*, 1997, **190**, 132.

9. For leading references see: X. Fang, M. Johannsen, S. Yao, N. Gathergood, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, 1999, **64**, 4844. See also W. Qiu, V. A. Soloshonok, C. Cai, X. Tang, and V. J. Hruby, *Tetrahedron*, 2000, **56**, 2577.

10. a) S. M. Weinreb, D. T. Smith, and J. Jin, *Synthesis* 1998, 509. b) J. Jin and S. M. Weinreb, *J. Am. Chem. Soc.* 1996, **118**, 3584. c) D. M. Tschaen, E. Turos, and S. M. Weinreb, *J. Org. Chem.* 1984, **49**, 5058. d) D. M. Tschaen and S. M. Weinreb, *Tetrahedron Lett.*, 1982, **23**, 3015.

11) a) K. Mikami, M. Kaneko, and T. Yajima, *Tetrahedron Lett.*, 1993, **34**, 4841. b) L. F. Tietze and M. Bratz, *Synthesis*, 1989, 439. c) J. H. Tidwell and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 11797.

12) W. J. Drury III, D. Ferraris, C. Cox, B. Young, and T. Lectka, *J. Am. Chem. Soc.*, 1998, **120**, 11006.

13. F. A. Davis and W. McCoull, *J. Org. Chem.* 1999, **64**, 3396.

14. G. Luisi and F. Pinnen, *Arch. Pharm.*, 1993, **326**, 139.

15. For recent applications of the sulfinimine-mediated asymmetric Strecker synthesis see:) F. A. Davis and V. Srirajan, *J. Org. Chem.*, 2000, **65**, 3248. b) F. A. Davis, S. H. Lee, Zhang, and D. L. Fanelli, *J. Org. Chem.*, 2000, **65**, 8704. c) F. A. Davis, H. Zhang, and S. H. Lee, *Org. Lett.*, 2001, **3**, 759.

16. a) F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli, and H. Zhang, *J. Org. Chem.*, 1999, **64**, 1403. b) D. L. Fanelli, J. M. Szewczyk, Y. Zhang, G. V. Reddy, D. M. Burns, and F. A. Davis, *Organic Syntheses*, 1999, **77**, 50.

17. For an example of the coordination of $SnCl_4$ with a C-C double bond see M. A. I. El-Erian, P. G. Huggett, and K. Wade, *Polyhedron*, 1991, **10**, 2131.

18. S. Kohji, B. Kenji, N. Shin-ichiro, and T. Toshikatsu, *Tetrahedron Lett.*, 1999, **40**, 7273.