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THE SYNTHESIS OF SPIROOXINDOLE PYRROLIDINES *VIA* AN ASYMMETRIC AZOMETHINE YLIDE [1,3]-DIPOLAR CYCLOADDITION REACTION

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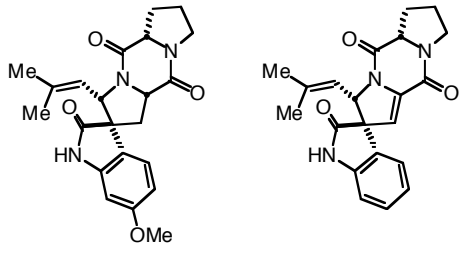
Abstract—The asymmetric [1,3] dipolar cycloaddition reactions of azomethine ylides derived from 5,6-diphenylmorpholin-2-one with various aldehydes and ethyl oxindolylideneacetate are described. Addition of an aldehyde to the morpholin-2-one, under essentially neutral conditions, results in the preferential formation of the *E*-ylide which then reacts with the dipolarophile to yield spirooxindole pyrrolidine derivatives in moderate to excellent regio- and diastereoselectivities. The resulting cycloadducts were easily separated by column chromatography and converted to the corresponding amino acid methyl esters through catalytic hydrogenolysis.

INTRODUCTION

The [1,3] dipolar cycloaddition reactions of azomethine ylides with alkene dipolarophiles have proven invaluable for the construction of highly substituted pyrrolidine derivatives.[1] Chiral pyrrolidines constitute the main structural element of a number of alkaloid natural products, including the microtubule inhibitors spirotryprostatins A and B (Figure 1).[2] The development of a general, stereoselective version of the reaction, either through the use of a chiral auxiliary attached to the dipolarophile or through the use of a chiral azomethine ylide is therefore an important synthetic objective.

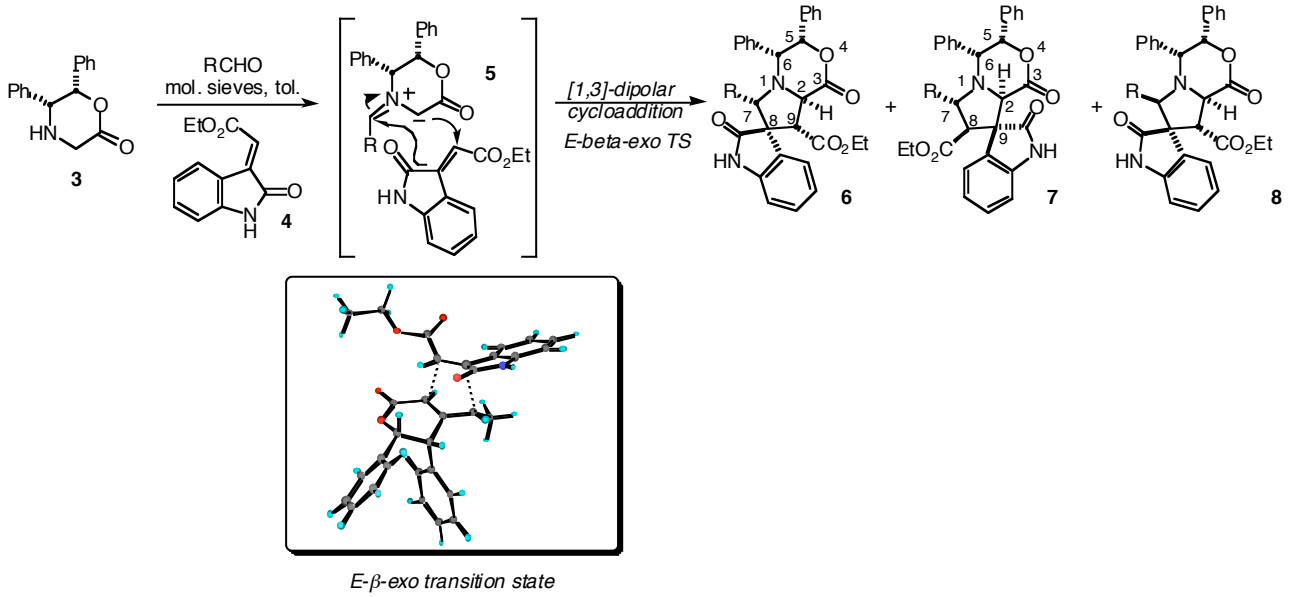


1, spirotryprostatin A **2**, spirotryprostatin B

Figure 1

Dedicated to Professor A. I. Meyers on the occasion of his 70th birthday.

Azomethine ylides derived from chiral, non-racemic glycinates have been shown to serve as effective templates for the synthesis of highly substituted pyrrolidines.[3] While a number of groups have explored the reaction of achiral azomethine ylides with oxindolylidene acetates,[4] to our knowledge there are no examples reported in the literature of [1,3] dipolar cycloaddition reactions between azomethine ylides derived from 5,6-diphenylmorpholin-2-one and oxindolylideneacetates. In our total synthesis of (-)-spirotryprostatin B, we demonstrated the viability of this approach for the formation of spirooxindole pyrrolidine derivatives.[5] In a continuation of this work, the effects of various aldehydes on the regio- and diastereoselectivity of this system and conversion of the cycloadducts to the corresponding amino acid methyl esters has been explored (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

The starting material for this investigation, (*5R,6S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (**3**), was conveniently prepared[6] from the commercially available *N-t*-BOC derivative.[7] Addition of an aldehyde to the amino lactone (**3)** in the presence 3Å molecular sieves in toluene generates an *E*/*Z* mixture of azomethine ylide (**5**). We have previously reported that in the case of sterically demanding aldehydes, the *E*-ylide was preferentially favored and that dipolar cycloadditions of ylides generated from this system proceeded with a high degree of *endo*-selectivity to give substituted pyrrolidines.[6] In the present system, the [1,3] dipole reacts with ethyl oxindolylidene acetate (**4**) *via* an *E-β-exo* transition state to yield spirooxindole cycloadducts (**6**) (Scheme 1). *E-β-exo* refers to the preferential formation of the *E*-azomethine ylide and approach of the dipolarophile *anti*- or *β*- to the phenyl groups with the carboethoxy

acting in an *exo*-fashion (inset, Scheme 1). Two other products were also isolated, **7** and **8**, and were the consequence of approach of the dipolarophile in an *endo*-fashion and *via* cycloaddition with the *Z*-ylide, respectively. The specific examples, reaction temperature, yields and diastereomeric ratios for **6**:**8** are recorded in Table 1.

Table 1. Spirooxindole Pyrrolidine Cycloadducts (**6**, **7** and **8**).

Entry	Aldehyde	R	Temp	Yield (% **6**)	Yield (% **7**)	Yield (% **8**)	Diast. ratio (**6**:**8**)
a	paraformaldehyde[a]	H	reflux	28	11	0	-
b	benzyloxy-acetaldehyde	$BzOCH_2$	reflux	44	14	0	>20:1
c	benzyloxy-acetaldehyde	$BzOCH_2$	60°C	54	8	0	>20:1
d	isobutyraldehyde	*i*-Pr	reflux	43	11	5	8.6:1
e	isobutyraldehyde	*i*-Pr	60°C	74	6	trace	>20:1
f	isovaleraldehyde	*i*-Bu	reflux	84	1	0	>20:1
g	isovaleraldehyde	*i*-Bu	60°C	86	0	0	>20:1
h	3-methoxy-3-methylbutanal[b]	$(Me)_2(OMe)CCH_2$	reflux	29	0	0	>20:1
i	3-methoxy-3-methylbutanal[c]	$(Me)_2(OMe)CCH_2$	60°C	82	1	0	>20:1
j	*p*-anisaldehyde[d]	*p*-MeOPh	reflux	60	0	0	>20:1

a) In addition, 9% of another compound was isolated, which was the result of addition of the dipolarophile in a regiochemically similar fashion to **7**, but with the carboethoxy group adding via an *exo*-approach. b) A second product (59%) was obtained as a result of elimination of the tertiary alcohol to afford the trisubstituted olefin derivative. c) The trisubstituted olefin was also obtained at 60°C for **6g**, although in reduced yield (6%). d) The reaction required prolonged heating (>24 h) to obtain the reported yield, whereas most reaction were complete between 2 and 8 h.

The regio- and stereochemistry of the resulting cycloadducts was dependent on the nature of the aldehyde constituents. Bulky aldehydes favored the formation of *E*-ylides and therefore cycloadducts (**6**), (Table 1, Entries f-j). *Ab initio* calculations on this system as well as a similar system[8] are in agreement with this observation. Isobutyraldehyde was expected to follow this trend, however the reaction produced three products, (**6d**, **7d** and **8d**) and resulted in an 8.6:1 diastereomeric ratio of **6d**:**8d**. For the less branched

systems, high diastereoselectivity resulted (>20:1), however only moderate *exo*-selectivity with respect to the carboethoxy group (*endo* for the oxindole) was observed, (Table 1, Entries a-c). The ylide generated from paraformaldehyde yielded three products, one of which was the result of the ester reacting in an *endo*-fashion, (**7a**). The more sterically demanding aldehydes resulted in high *exo*-selectivity as well as high diastereoselectivity (Table 1, Entries f-j).

Reaction temperature also seemed to affect the regiochemistry and stereochemistry of the resulting products. In the case of isobutyraldehyde moderate regioselectivity and diastereoselectivity was observed when the reaction was performed under refluxing toluene conditions. When the temperature of the system was lowered to 60 ^{o}C, the ratio of cycloadducts (**6**) and (**7**) was increased from ~4:1 to ~12:1 and the diastereomeric ratio of products (**6**) and (**8**) improved to greater than 20:1 (Table 1, Entries d and e). On the contrary, cycloaddition of the ylide derived from *p*-anisaldehyde (Entry j), required refluxing conditions for the reaction to occur. Presumably, the electron-donating effect of the methoxy group deters attack of the aldehyde by the incoming nucleophile and requires elevated temperatures for the formation of the azomethine ylide.

The regiochemistry of the cycloadducts were easily determined by the mutiplicity of the C2 hydrogen; a doublet was observed in the case of cycloadducts (**6**) and (**8**) whereas as singlet is exhibited for cycloadduct (**7**). The relative and absolute stereochemistry was determined by difference nOe ^{1}H NMR spectroscopy and correlation to the known stereogenic centers (C5 and C6) of the starting material (*5R*,*6S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (Figure 2). The structure of Entry **6i** was confirmed by single crystal X-Ray analysis as reported in the earlier account of the total synthesis of spirotryprostatin B.

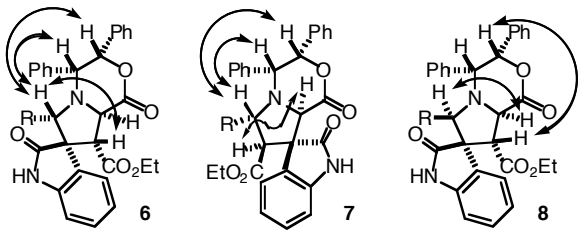
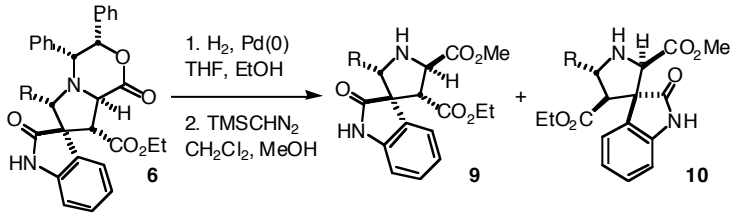


Figure 2. Observed nOe enhancements for cycloadducts (**6**, **7** and **8**).

Conversion of the tetracyclic products into the corresponding spirooxindole-substituted proline methyl ester derivatives was accomplished by catalytic hydrogenation (Scheme 2). For characterization purposes, the amino acids were converted to the corresponding methyl esters. Hydrogenolysis of the chiral auxiliary was accomplished in most cases by the use of palladium chloride under 70 psi of hydrogen for 36 hs (Table 2). However, *p*-anisaldehyde derivative (**6j**) proved resistant to these conditions and only partial

reduction was observed, (Table 2, Entry 5). Elevated temperatures and pressures resulted in a complex mixture of products. Pearlman's catalyst, which has been shown to selectively reduce the benzylic C-N bond of an unsubstituted aromatic in the presence of a *p*-methoxy derivative,[9] failed to dramatically improve formation of the desired product. The bulk of the reaction proved again, to be under-reduction. A search for alternative sources of Pd(0) yielded conditions[10] for the complete removal of the bibenzyl moiety (Table 2, Entry 7). Small amounts of epimerization at the α-position and cleavage of the pyrrolidine C-N bond were observed along with 59% of the desired product for the two steps. It is noteworthy to mention that any attempt to remove the chiral auxiliary *via* an oxidative protocol, such as $Pb(OAc)_4$ or $NaIO_4$ resulted in decomposition of the starting material. The electron-rich oxindole moiety presumably reacts with the oxidizing agents examined.



Scheme 2

Table 2. Conversion of dipolar cycloadducts (**6**) into amino acids methyl esters (**9**) and (**10**).

Entry	Substrate	Method	Yield (% **9** and **10**)
1	**6a**	H_2, $PdCl_2$	93
2	**7a**	H_2, $PdCl_2$	73
3	**6f**	H_2, $PdCl_2$	89
4	**6h**	H_2, $PdCl_2$	85
5	**6j**	H_2, $PdCl_2$	5
6	**6j**	H_2, $Pd(OH)_2$	25
7	**6j**	H_2, Pd-C, 1N HCl	59

CONCLUSION

In summary, the asymmetric syntheses of spirooxindole-substituted pyrrolidines *via* diastereoselective [1,3] dipolar cycloaddition of azomethine ylides derived from a chiral, non-racemic glycinate and ethyl oxindolylidene are described. The reaction is highly *exo*-selective for the carboethoxy group of the dipolarophile and sets three or four contiguous stereogenic centers including the quaternary carbon of a spirooxindole. In most cases two regioisomers were detected and were isolated with good to excellent diastereoselectivity. This methodology should find uslefu applications for the synthesis of

spirooxindole-substituted natural products and their derivatives.

ACKNOWLEDGMENT

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EXPERIMENTAL

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120°C) that was cooled in a dessicator, unless stated otherwise. Toluene was freshly distilled from CaH_2. THF was freshly distilled from sodium benzophenone ketyl. 3Å molecular sieves were activated by heating for three minutes at the highest setting in a microwave followed by cooling under argon. Column chromatography was performed on Merck silica gel Kiesel 60 (230-400 mesh). ^1H NMR, ^{13}C NMR, HSQC and nOe experiments were recorded on a Varian 400 MHz spectrometer. Spectra were recorded in $CDCl_3$ and chemical shifts (δ) were given in ppm and were relative to $CHCl_3$. MS were obtained on Fisons VG Autospec. IR spectra were recorded on a Perkin-elmer 1600 series FT-IR spectrophotometer. Optical rotations were determined with a Rudolph Research Autopol III automatic polarimeter referenced to the D-line of sodium.

General procedure for the [1,3] dipolar cycloaddition of oxindolyl acetates with azomethine ylides derived from (5*R*,6*S*)-5,6-diphenylmorpholin-2-one:

Method A (Reflux): To a flame dried 25 mL round bottom with stir bar was added (*5R*,*6S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (253 mg 1.0 mmol), ethyl oxindolyl acetate (325 mg, 1.5 mmol) and 0.50 g of activated 3Å molecular sieves. An oven-dried condensor was attached and the system was flushed with Ar. Freshly distilled toluene (10 mL) followed by the aldehyde (1.2 mmol). The system was heated to reflux under Ar and kept at that temperature for two hs. The system was allowed to cool to rt, filtered through celite to remove the sieves and purified by flash chromatography using hexane/EtOAc as the eluents. Analytical samples were prepared by HPLC.

Method B (60°C): To a flame dried 25 mL round bottom with stir bar was added (*5R*,*6S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (253 mg 1.0 mmol), ethyl oxindolylacetate (325 mg, 1.5 mmol) and 0.50 g of activated 3Å molecular sieves. The system was flushed with Ar. Freshly distilled toluene (10 mL) was added followed by the aldehyde (1.2 mmol). The system was warmed to 60°C under Ar, as measured by a thermocouple, and kept at that temperature for 2h. The reaction was allowed to cool to rt, filtered through celite to remove the sieves and purified by flash chromatography using hexane/EtOAc as the eluents. Analytical samples were prepared by HPLC.

Cycloaddition of azomethine ylide derived from paraformaldehyde. Method B: From 360 mg of paraformaldehyde (10.0 mmol) was obtained 135 mg of **6a** (28%), 53 mg of **7a** (11%), and 43 mg of **7a-*exo*** (9%) as white amorphous solids after refluxing for 10 h and purification by flash chromatography on silica gel (2:1 hexanes:ethyl acetate). For **6a:** $[\alpha]_D^{25}$ = -32.0° (*c* 0.78, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 7.27–7.21 (m, 10H), 7.09 (dd, J=1.6 Hz, 6.8 5.75 (d, J=4.0 Hz, 1H), 4.98 (d, J=8.8 Hz, 1H), 4.54 (d, J=4.0 Hz, 1H), 4.15 (d, J=8.8 Hz, 1H), 3.87-3.81 (m, 1H), 3.75-3.69 (m, 1H), 3.20 (d, J=9.6 Hz, 1H), 3.08 (d, J=9.6 Hz, 1H), 0.72 (t, J=6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.2, 171.4, 168.7, 140.8, 136.1, 134.4, 129.8, 129.1, 128.8, 128.7, 128.4, 127.9, 124.6, 123.2, 110.1, 84.4, 67.5, 63.7, 61.4, 60.7, 55.5, 54.3, 13.6;. **IR** (neat) 3302, 1735, 1618; **HRMS** (FAB+) Calcd for $C_{29}H_{27}N_2O_5$ (*m*/*z*) 483.1920, found 483.1917; **NOE** data: irradiation of H_6 enhanced H_7-α: (3.45%); irradiation of H_7-α enhanced H_9 (3.61%). For **7a:** $[\alpha]_D^{25}$ = - 111.0° (*c* 1.09, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.23–7.13 (m, 9H), 7.02 (t, J = 7.6 Hz, 1H), 7.04-6.97 (m, 2H), 6.88 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 2H), 5.52 (d, J = 4.0 Hz, 1H), 5.02 (d, J = 4.0 Hz, 1H), 4.77 (s, 1H), 3.70-3.60 (m, 2H), 3.56 (dd, J = 6.4 Hz, J = 10.8 Hz, 1H), 3.46 (t, J = 10.8 Hz, 1H), 3.32 (dd, J = 6.4 Hz, J = 10.8 Hz, 1H), 0.68 (t, J=6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.7, 169.8, 167.9, 141.5, 135.4, 134.7, 130.3, 129.4, 129.3, 128.6, 128.5, 128.4, 127.6, 123.7, 123.0, 110.2, 86.2, 72.9, 62.6, 61.6, 60.9, 54.1, 51.5, 13.6. **IR** (neat) 3307, 1726, 1620 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{29}H_{27}N_2O_5$ (*m*/*z*) 483.1920, found 483.1911. For **7a–*exo*:** $[\alpha]_D^{25}$ = -123.0° (*c* 0.43, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.33 (d, J=7.2 Hz, 1H), 7.23–6.95 (m,12H), 6.88 (d, J=7.2 Hz, 1H), 5.69 (d, J=4.0 Hz, 1H), 4.67 (d, J=4.0 Hz, 1H), 4.54 (s, 1H), 3.75-3.60 (m, 2H), 3.60 (t, J=8.4 Hz, 1H), 3.51 (t, J=9.2 Hz, 1H), 3.25 (t, J=9.2 Hz, 1H), 0.68 (t, J=7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.9, 169.2, 166.7, 142.2, 134.7, 133.5, 129.5, 129.4, 128.6, 128.4, 128.1, 127.9, 127.0, 124.4, 122.8, 110.1, 85.6, 68.7, 65.4, 61.1, 58.3, 52.5, 50.0, 13.5; **IR** (neat) 3313, 1731, 1619 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{29}H_{27}N_2O_5$ (*m*/*z*) 483.1920, found 483.1904; **NOE** data: irradiation of H_2 enhanced H_8 (1.54%).

Cycloaddition of azomethine ylide derived from benzyloxyacetaldehyde. Benzyloxyacetaldehyde (180 mg, 1.2 mmol) was prepared according to literature procedure.[11] **Method A:** 265 mg of **6b** (44%) and 85 mg of **7b** (14%) were obtained as white amorphous solids. **Method B:** 325 mg of **6b** (54%) and 50 mg of **7b** (8%) were obtained as white amorphous solids. For **6b:** $[\alpha]_D^{25}$ = -32.5° (*c* 0.56, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 7.24-6.95 (m, 18H), 6.85 (d, J=7.6 Hz, 1H), 4.89 (d, J=8.0 Hz, 1H), 4.75 (d, J=3.2 Hz, 1H), 4.12-4.05 (m, 3H), 4.00 (d, J=8.0 Hz, 1H), 3.77-3.73 (m, 1H), 3.73-3.65 (m, 1H), 3.23 (dd, J = 6.0 Hz, J = 9.6 Hz, 1H), 3.06 (dd, J=4.2 Hz, J = 9.6 Hz, 1H), 0.68 (t, J=7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 171.4, 168.2, 141.4, 137.4, 136.4, 135.8, 129.3, 129.1, 128.5, 128.4, 128.0, 127.9, 127.8, 126.2, 126.1, 122.8, 109.9, 78.2, 73.7, 70.9, 69.9, 62.2, 61.5, 58.6, 58.2, 54.5, 13.6; **IR** (neat) 3269, 1732, 1618 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{37}H_{35}N_2O_6$ (*m*/*z*) 603.2495, found 603.2477; **NOE** data: irradiation of H_6 enhanced H_7 (3.07%). For **7b:** $[\alpha]_D^{25}$ = -161.8° (c 0.22, $CHCl_3$); **^{1}H NMR** (400 MHz, CDCl3) δ 7.69 (br s, 1H), 7.34 (d, J=7.2 Hz, 1H), 7.22-7.12 (m, 12H) 7.04-6.98 (m, 4H), 6.86 (t, J = 7.2 Hz, 2H), 5.61 (d, J = 3.6 Hz, 1H), 5.06 (s, 1H), 4.87 (d, J = 3.6 Hz, 1H), 4.37 (1/2ABq, J = 12.0 Hz, 1H), 4.29 (1/2ABq, J = 12.0 Hz, 1H), 4.30-4.24 (m, 1H), 3.65-3.60 (m, 1H), 3.46 (dd, J = 4.0 Hz, J = 9.6 Hz, 1H), 3.36 (dd, J = 4.8 Hz, J = 9.6 Hz, 1H), 0.66 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl3) δ 177.0, 169.0, 167.0, 142.2, 138.2, 136.0, 135.3, 129.7, 129.6, 128.6, 128.5, 128.2, 128.1, 127.6, 127.1, 124.6, 122.7, 110.4, 83.5, 73.3, 72.3, 69.9, 65.5, 64.1, 61.1, 60.2, 52.9, 13.5; **IR** (neat) 3269, 1732, 1618 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{37}H_{35}N_2O_6$ (m/z) 603.2495, found 603.2483.

Cycloaddition of azomethine ylide derived from isobutyraldehyde. Isobutyraldehyde (86 mg, 1.2 mmol) was used as received from Aldrich. **Method A:** 225 mg of **6c** (43%), 73 mg of **7d** (11%) and 25 mg of **8d** (5%) were obtained as white amorphous solids. Method B: 387 mg of **6d** (74%), 30 mg of **7d** (6%) and a trace amount of **8d** (<1%) were obtained as white amorphous solids. For **6d:** $[\alpha]_D^{25}$ = -58.8° (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.31–7.16 (m, 10 H), 7.08–6.91 (m, 4H), 6.19 (d, J = 4.0 Hz, 1H), 5.12 (d, J = 13.2 Hz, 1H), 4.36 (d, J = 4.0 Hz, 1H), 3.86 (d, J = 13.2 Hz, 1H), 3.85-3.73 (m, 3H), 1.88 (sept, J = 9.2 Hz, 1H), 0.86 (d, J = 9.2 Hz, 3H), 0.81 (t, J = 9.6 Hz, 3H), 0.63 (d, J=9.2 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl3) δ 178.3, 170.1, 167.2, 140.9, 136.0, 135.7, 129.5, 129.0, 128.5, 128.2, 127.8, 127.6, 126.3, 126.1, 122.7, 110.1, 77.5, 76.4, 64.3, 61.5, 59.8, 59.5, 56.8, 30.8, 20.5, 19.2, 13.7;. **IR** (neat) 3288, 1729, 1618 cm^{-1}; HRMS (FAB+) Calcd for $C_{32}H_{33}N_2O_5$ (m/z) 525.2389, found 525.2390. NOE data: irradiation of H9 enhanced H5 (2.62%). For **7d**: $[\alpha]_D^{25}$ = -20.7° (c 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz, CDCl3) δ 7.87 (br s,1H), 7.43 (d, J = 10.0 Hz, 1H), 7.37–7.03 (m, 9H), 6.97-6.83 (m, 4H), 5.59 (d, J = 4.8 Hz, 1H), 5.03 (s, 1H), 4.71 (d, J = 4.8 Hz, 1H), 4.14 (dd, J = 6.0, J = 12.0 Hz, 1H), 3.74-3.63 (m, 2H), 3.60 (d, J = 12.0 Hz, 1H), 1.86-1.80 (m, 1H), 0.96 (d, J = 9.2 Hz, 3H), 0.68 (t, J = 6.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.3, 169.8, 167.1, 142.4, 136.2, 135.2, 129.7, 129.6, 128.7, 128.3, 128.1, 128.0, 127.8, 126.8, 125.4, 122.5, 110.6, 84.4, 71.2, 71.1, 64.9, 61.9, 61.1, 51.7, 32.0, 18.6, 17.0, 13.5;. **IR** (neat) 3300, 1727, 1618 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{32}H_{33}N_2O_5$ (*m*/*z*) 525.2389, found 525.2378; **NOE** data: irradiation of H_5 enhanced H_7 (4.16%). For **8d:** $[\alpha]_D^{25}$ = -24.0° (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.32–7.21 (m, 10H), 7.06–7.04 (m, 2H), 6.94 (t, J = 10.4 Hz, 1H), 6.89 (d, J = 10.0 Hz, 1H), 6.68 (d, J = 10.0 Hz, 1H), 6.50 (d, J = 5.2 Hz,

1H), 4.81 (d, J = 5.2 Hz, 1H), 4.74 (d, J = 14.0 Hz, 1H), 3.90 (d, J = 14.0 Hz, 1H), 3.80-3.69 (m, 2H), 3.21 (d, J = 10.4 Hz, 1H), 2.51 (sept, J = 9.2 Hz, 1H), 0.88 (d, J = 10.4 Hz, 3H), 0.79 (d, J = 10.4 Hz, 3H), 0.74 (t, J = 9.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.8, 168.6, 140.3, 140.9, 136.2, 133.9, 130.9, 129.7, 128.8, 128.2, 128.1, 127.8, 126.1, 125.0, 122.9, 109.7, 82.7, 77.4, 61.3, 61.1, 60.6, 58.6, 57.0, 28.1, 20.6, 18.9, 13.6;. **IR** (neat) 3296, 1734, 1715, 1618 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{32}H_{33}N_2O_5$ (*m*/*z*) 525.2389, found 525.2386; **NOE** data: irradiation of H_5 enhanced H_9 (6.88%); irradiation of H_7 enhanced H_2 (4.30%).

Cycloaddition of azomethine ylide derived from isovaleraldehyde. Isovaleraldehyde (103 mg, 1.2 mmol) was used as received from Aldrich. **Method A:** 452 mg of **6f** (84%) was obtained as white amorphous solids and a trace amount of **7f** (~1%) was observed in the ^{1}H NMR spectra but not isolated. **Method B:** 463 mg of **7f** (86%) was obtained as a white amorphous solid. For **7f:** $[\alpha]_D^{25}$ = +62.7^o (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 7.31–7.20 (m, 12H), 7.00 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.11 (d, J = 3.2 Hz, 1H), 6.50 (d, J = 5.2 Hz, 1H), 4.87 (d, J = 8.0 Hz, 1H), 4.48 (d, J = 3.2 Hz, 1H), 3.99 (d, J = 8.0 Hz, 1H), 3.81-3.64 (m, 3H), 1.34-1.17 (m, 2H), 1.00-0.93 (m, 3H), 0.74 (d, J = 6.4 Hz, 3H), 0.70 (d, J = 7.2 Hz, 3H), 0.62 (t, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.2, 171.5, 168.4, 141.4, 136.3, 136.0, 129.2, 129.1, 128.6, 128.5, 128.2, 128.0, 126.6, 126.5, 126.2, 122.9, 109.9, 77.6, 68.8, 61.5, 60.8, 59.8, 58.2, 54.8, 39.9, 25.8, 23.7, 22.6, 13.6;. **IR** (neat) 3284, 1732, 1618 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{33}H_{35}N_2O_5$ (*m*/*z*) 539.2546, found 539.2544; **NOE** data: irradiation of H_5 enhanced H_9 (2.17%).

Cycloaddition of azomethine ylide derived from 3-methyl-3-methoxybutanal. 3-Methyl-3-methoxybutanal (116 mg, 1.2 mmol) was prepared by Swern oxidation of 3-methyl-3-methoxybutan-ol, which is commercially available from Aldrich. **Method A:** 165 mg of **6h** (29%) and 335 mg of **6h-*elim*** (59%) were obtained as white amorphous solids. **Method B:** 465 mg of **6h** (82%), 34 mg of **6h-*elim*** (6%) and 5 mg of **7h** (1%) were obtained as white amorphous solids. For **6h:** $[\alpha]_D^{25}$ = -14.0^o (c 1.0, CH_2Cl_2); melting point: 225-227 ^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.18-7.33 (m, 10H), 7.15 (d, J = 7.5 Hz, 1H), 7.00 (dt, J = 0.9 Hz, 7.5Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.40 (d, J=3.3 Hz, 1H), 5.07 (d, J = 3.3 Hz, 1H), 4.65 (d, J = 7.5 Hz, 1H), 4.04 (t, J = 3.3 Hz, 1H), 3.95 (d, J = 7.5 Hz, 1H), 3.63-3.85 (m, 2H), 3.08 (s, 3H), 1.70 (d, J = 3.3 Hz, J = 15.9 Hz, 2H), 1.14 (dd, J = 3.6 Hz, J = 16.2 Hz, 2H), 1.09 (s, 6 H), 0.68 (t, J = 6.9, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ $CHCl_3$: 178.9, 173.0, 170.1, 142.3, 138.3, 137.5, 130.4, 130.2, 129.5, 129.4, 128.5, 128.4, 128.3, 127.2, 126.2, 124.0, 110.8, 77.1, 74.5, 65.5, 61.5, 57.5, 57.1, 56.0, 53.3, 50.6, 45.4, 26.9, 23.6; I**R** (NaCl/neat) 3308, 1734, 1618 cm^{-1};

An X-Ray crystal structural analysis for this compound has been previously reported.[5] For **6h-*elim*: [α]$_D^{25}$** = +52.8° (c 0.95, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.01-7.35 (m, 12H), 6.84 (d, J = 7.6 Hz, 2H), 6.41 (d, J = 2.8 Hz, 1H), 5.0 (s, 1H), 4.69 (d, J = 7.6 Hz, 1H), 4.53 (m, 1H), 4.00-4.14 (m, 2H), 3.41 (d, J = 6.0 Hz, 1H), 3.18 (s, 3H), 1.80-1.94 (m, 2H), 1.19 (s, 3 H), 1.16 (s, 3 H), 1.11 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.6, 171.8, 168.6, 141.4, 136.4, 136.0, 129.2, 129.0, 128.6, 128.3, 128.1, 127.8, 126.9, 126.1, 125.9, 122.7, 119.8, 109.8, 78.0, 68.7, 61.4, 60.2, 59.8, 57.3, 54.1, 26.2, 18.8, 13.5; **IR** (NaCl/neat) 3305, 1730, 1618 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{33}H_{33}N_2O_5$ (*m*/*z*) 537.2389, found 537.2383. For **7h: [α]$_D^{25}$** = +118.1° (c 1.05, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.16-7.28 (m, 12H), 6.97, (t, J = 6.8 Hz, 1H), 6.84 (d, J = 6.8 Hz, 1H), 6.08 (d, J = 3.6 Hz, 2H), 5.0 (s, 1H), 4.87 (d, J = 7.6 Hz, 1H), 4.51 (s, 1H), 4.50 (t, J = 7.6 Hz, 1H), 4.36 (d, J = 3.6 Hz, 1H), 4.04 (d, J = 7.6 Hz, 1H), 3.78-3.83 (m, 1H), 3.46-3.68 (m, 1H), 1.67 (s, 3H), 1.42 (s, 3H), 0.64 (t, J = 6.8, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ $CHCl_3$: 179.4, 170.4, 169.5, 141.1, 137.1, 137.0, 129.4, 129.2, 128.3, 128.0, 127.8, 127.7, 127.4, 126.5, 124.7, 123.1, 110.3, 79.2, 73.7, 65.6, 60.7, 60.5, 60.4, 59.8, 56.1, 49.5, 43.0, 24.8, 24.7, 14.2; **IR** (NaCl/neat) 3288, 1718, 1621 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{33}H_{37}N_2O_6$ (*m*/*z*) 569.2652, found 569.2640.

Cycloaddition of azomethine ylide derived from *p*-anisaldehyde. *p*-Anisaldehyde (163 mg, 1.2 mmol) was used as received from Aldrich. **Method A:** 353 mg of **6j** (60%) was obtained as white amorphous solid. For **6j: [α]$_D^{25}$** = +80.8° (*c* 0.47, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.26–7.04 (m, 15H), 6.91 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 7.6 Hz, 2H), 6.22 (d, J = 3.2 Hz, 1H), 5.12 (d, J = 8.0 Hz, 1H), 4.95 (s, 1H), 4.17 (d, J = 3.2 Hz, 1H), 4.09 (d, J = 8.0 Hz, 1H), 3.87-3.79 (m, 1H), 3.72-3.64 (m, 4H), 0.63 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.8, 171.6, 168.4, 140.6, 136.0, 135.8, 129.4, 129.1, 129.0, 128.6, 128.4, 127.9, 126.8, 126.0, 125.7, 125.6, 122.4, 113.8, 109.6, 76.2, 74.6, 61.5, 61.4, 59.0, 57.1, 55.3, 54.4, 13.5; **IR** (neat) 3296, 1728, 1612 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{36}H_{33}N_2O_6$ (*m*/*z*) 589.2338, found 589.2327; **NOE** data: irradiation of H_7 enhanced H_5 (10.2%) and H_9 (4.38%)

General procedure for the reduction of spirooxindole pyrrolidine derivatives to the corresponding amino acid methyl esters: The cycloadducts (0.1 mmol) were taken up in THF:MeOH 1:1 (2 mL) and transferred to a pressurizable tube. Argon was bubbled through for 5 min and $PdCl_2$ (18 mg, 0.1 mmol) added. The system was sealed and hydrogenated (65-75 Psi) for 36 h at rt. The heterogeneous solution was filtered through celite and evaporated under reduced pressure. The resulting oil was taken up in CH_2Cl_2:MeOH 1:1 (2 mL), a stir bar added and $TMSCHN_2$, available from Aldrich as a 2.0 M solution in hexanes, was added until a yellow color persisted. The reaction was stirred for 15 min and then

evaporated under reduced pressure. Purification by flash chromatography using hexanes/EtOAc as the eluents yielded white amorphous solids. Analytical samples were prepared by PTLC.

Amino acid methyl ester (9a): Prepared by hydrogenation of cycloadduct (**6a)** (50 mg, 1.0 mmol). Column chromatography with 2:1 hexanes:EtOAc yielded 30 mg (93%) of **9a** as a white amorphous solid. For **9a:** $[\alpha]_D^{25}$ = -23.0^o (*c* 0.40, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 4.62 (d, J = 7.6 Hz, 1H), 3.82-3.73 (m, 1H), 3.79 (s, 3H), 3.73-3.68 (m, 1H), 3.47 (1/2ABq, J = 10.8 Hz, 1H), 3.10 (1/2ABq, J = 10.8 Hz, 1H), 2.76 (br s, 1H), 0.69 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.1, 173.5, 169.6, 140.6, 130.1, 128.9, 124.4, 123.0, 109.7, 62.3, 61.2, 58.5, 58.0, 56.6, 52.9, 13.6; **IR** (neat) 3303, 1732, 1618 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{16}H_{19}N_2O_5$ (*m*/*z*) 319.1294, found 319.1286.

Amino acid methyl ester (10a): Prepared by hydrogenation of cycloadduct (**7a)** (50 mg, 1.0 mmol). Column chromatography with 2:1 hexanes:EtOAc yielded 24 mg (73%) of **10a** as a white amorphous solid. For **10a:** $[\alpha]_D^{25}$ = -61.1^o (*c* 0.61, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 7.19 (dt, J = 0.8 Hz, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.94 (dt, J = 0.8 Hz, J = 7.6 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 4.34 (s, 1H), 3.87-3.63 (m, 4H), 3.53 (dd, J = 8.4 Hz, J = 10.8 Hz, 1H), 3.23 (s, 3H), 2.76 (br s, 1H), 0.70 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.4, 170.2, 169.7, 141.3, 129.2, 127.0, 124.6, 122.7, 109.6, 70.2, 61.0, 59.6, 54.2, 52.1, 47.8, 13.6; **IR** (neat) 3326, 1730, 1615 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{16}H_{19}N_2O_5$ (*m*/*z*) 319.1294, found 319.1289.

Amino acid methyl ester (9f): Prepared by hydrogenation of cycloadduct (**6f)** (50 mg, 0.9 mmol). Column chromatography with 2:1 hexanes:EtOAc yielded 31 mg (89%) of **9f** as a white amorphous solid. For **9f:** $[\alpha]_D^{25}$ = +24.8^o (*c* 0.64, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.20 (dt, J = 1.2 Hz, J = 7.6 Hz, 1H), 6.98 (dt, J = 1.2 Hz, J = 7.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 3.84 (d, J = 6.8 Hz, 1H), 3.80-3.75 (m, 1H), 3.78 (s, 3H), 3.68-3.60 (m, 2H), 2.59 (br s, 1H), 1.50-1.45 (m, 1H), 0.95-0.87 (m, 1H), 0.79-0.72 (m, 1H), 0.76 (d, J = 6.8 Hz, 6H), 0.65 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.2, 174.9, 169.4, 141.1, 128.7, 127.5, 125.8, 122.7, 109.6, 65.5, 61.2, 59.3, 55.8, 52.9, 39.2, 25.8, 23.5, 22.2, 13.5; **IR** (neat) 3325, 1728, 1617 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{20}H_{27}N_2O_5$ (*m*/*z*) 375.1920, found 375.1922.

Amino acid methyl ester (9h): Prepared by hydrogenation of cycloadduct (**6h)** (50 mg, 1.0 mmol). Column chromatography with 2:1 hexanes:EtOAc yielded 30 mg (93%) of **9h** as a white amorphous

solid. For **9h:** $[\alpha]_D^{25}$ = -27.3° (c 0.97, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.18 (dt, J= 0.8 Hz, J = 7.6 Hz, 1H), 6.96 (dt, J = 0.8 Hz, J = 7.6 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 4.58 (d, J = 8.8 Hz, 1H), 3.80-3.72 (m, 1H), 3.76 (s, 3H), 3.70 (d, J = 8.8 Hz, 1H), 3.66-3.58 (m, 1H), 3.17 (br s, 1H), 3.08 (s, 3H), 1.19 (dd, J = 9.6 Hz, 14.4 Hz, 1H), 1.10 (s, 3H), 0.99 (s, 3H), 0.90 (dd, J = 1.6 Hz, J = 14.4 Hz, 1 H), 0.63 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.0, 175.2, 169.4, 140.9, 128.6, 127.8, 126.2, 122.7, 109.4, 74.4, 63.7, 61.1, 61.0, 59.1, 54.9, 52.8, 49.4, 40.6, 25.8, 24.4, 13.5; **IR** (neat) 3244, 1734, 1618 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{21}H_{29}N_2O_6$ (*m*/*z*) 405.2025, found 405.2024.

Amino acid methyl ester (9j): Prepared by hydrogenation of cycloadduct (**6j**) (50 mg, 1.0 mmol). Column chromatography with 2:1 hexanes:EtOAc yielded 30 mg (93%)of **9j** as a white amorphous solid. For **9j:** $[\alpha]_D^{25}$ = +30.8° (*c* 0.65, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (br s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.99 (t, J = 7.2 Hz, 1H), 6.53 (d, J = 8.8 Hz, 3H), 4.77 (d, J = 6.8 Hz, 3H), 4.73 (s, 1H), 3.96 (d, J = 6.8 Hz, 3H), 3.82-3.75 (m, 1H), 3.80 (m, 3H), 3.69-3.59 (m, 1H), 3.62 (m, 3H), 2.79 (br s, 1H), 0.69 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.4, 175.1, 169.3, 159.3, 140.4, 128.6, 128.3, 126.9, 126.5, 122.2, 113.1, 109.2, 70.1, 62.4, 61.2, 58.2, 55.2, 54.8, 52.9, 13.5; **IR** (neat) 3265, 1735, 1713, 1618 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{23}H_{25}N_2O_6$ (*m*/*z*) 425.1713, found 425.1706.

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