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Asymmetric dipolar cycloaddition reactions: a practical, convergent synthesis of chiral pyrrolidines

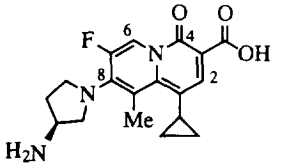
Zhenkun Ma,[a,*] Sanyi Wang,[a] Curt S. Cooper,[a] Anthony K. L. Fung,[a] John K. Lynch,[b] Frederick Plagge[b] and Daniel T. W. Chu[a]

[a] Anti-infective Research and Process Research, Abbott Laboratories, Abbott Park, IL 60064-3500, USA

[b] Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064-3500, USA

Abstract: Chiral *trans*-3,4-disubstituted pyrrolidines were obtained from the 1,3-dipolar cycloaddition of chiral α,β-unsaturated *N*-acyloxazolidinones and azomethine ylide.

Chiral pyrrolidines are common building blocks for many natural and unnatural compounds which possess important biological activity. One such class of compounds is the newly discovered 2-pyridones.[1] The 2-pyridones, exemplified by **ABT-719**, are novel DNA gyrase inhibitors which possess broad spectrum antibacterial activity. According to a proposed cooperative binding model, the C-8 substituent of 2-pyridones is an important part of the binding domain with gyrase.[2] Preliminary studies indicated that the structure and stereochemistry of the C-8 substituent have great impact on the antibacterial activity.[1] To further study the structure–activity relationships (SAR) regarding this C-8 position, we were interested in a series of analogs which possessed a *trans*-3-amino-4-alkylpyrrolidine moiety. We report here an asymmetric 1,3-dipolar cycloaddition reaction which leads to the convergent synthesis of such chiral pyrrolidines.



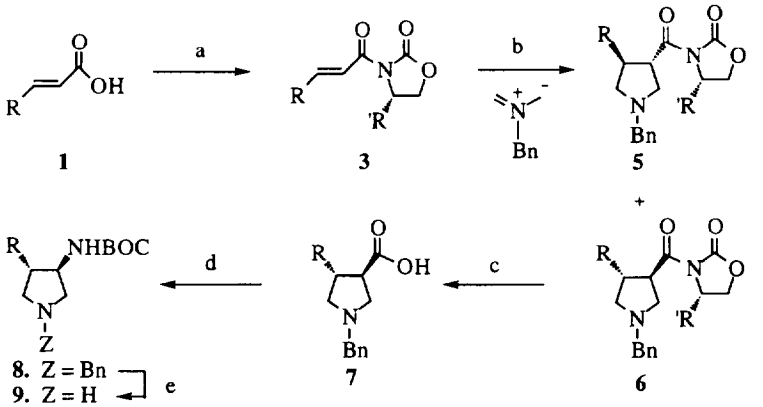
ABT-719

Among a wide range of approaches, the 1,3-dipolar cycloaddition of azomethine ylides to olefinic dipolarophiles represents one of the most convergent syntheses of substituted pyrrolidines.[3,4] This method has been studied extensively and is widely used in the synthesis of natural alkaloids and pharmaceuticals.[5] In contrast to the Diels–Alder cycloaddition, however, the asymmetric version of this powerful reaction employing a removable chiral auxiliary or catalyst has not been extensively explored.[6]

During our study, we employed chiral oxazolidinones as the asymmetric inducing element, which have been used successfully in asymmetric Diels–Alder reactions by Evans and others.[7] As shown in Scheme 1, the dipolarophiles **3** were easily prepared by coupling *trans*-α,β-unsaturated acids **1** and chiral oxazolidinones **2**. The oxazolidinone group serves three purposes: as chiral control element; as activator of the unreactive α,β-unsaturated acid; and it allows for facile chromatographic separation of the two diastereomeric pyrrolidinyl products. Since there is a wide availability of *trans*-α,β-unsaturated acids, a broad array of dipolarophiles with different β-substituents can be easily obtained.

Dipolar cycloaddition of **3** with *N*-benzyl-*N*-(methoxymethyl)-trimethylsilylmethylamine **4**[4a], catalyzed by trifluoroacetic acid, provided pyrrolidines **5** and **6** diastereoselectively in high yield. The

* Corresponding author.



(a) (i) oxalyl chloride, DMF, toluene, rt. (ii) (*S*)-(-)-4-substituted-2-oxazolidinone (**2**), *n*-BuLi, THF, -78 °C, 89 % in two steps. (b) *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (**4**), 0.1 eq TFA, toluene, 0 °C, 99 %. (c) LiOH, H_2O_2, THF-H_2O, rt, quantitative yield. (d) DPPA, Et_3N, *t*-BuOH, 95 °C, 80 %. (e) HCO_2NH_4, 10 % Pd-C, MeOH, reflux, quantitative yield.

(Stated yields are for R = cyclopropyl and R' = phenyl only)

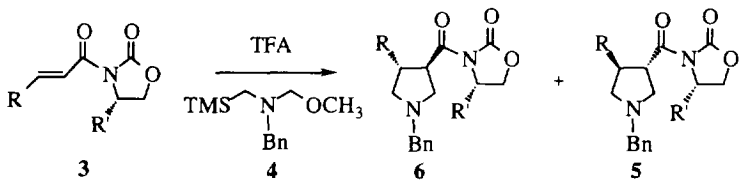
Scheme 1.

diastereoselectivity for the dipolar cycloaddition depended on the structure of the oxazolidinone as well as the reaction conditions (Table 1). Higher diastereoselectivity was achieved when the reaction was run in toluene instead of methylene chloride (entry 1 and 2, 5 and 6, 7 and 8). Of the three oxazolidinone auxiliaries examined, 4-phenyl-2-oxazolidinone gave the best selectivity (entry 4–9). Thus, under optimum conditions, reaction of **3** (R=cyclopropyl, R′=phenyl) and **4** provided diastereomeric pyrrolidines **5** and **6** in a ratio of 20:80 and a combined yield of 99% (entry 8). We have also explored other factors which could affect the reaction. At lower reaction temperatures (−40 °C) the reaction proceeded much more slowly without providing significant improvement in selectivity. Addition of a Lewis acid catalyst such as $Mg(OCOCF_3)_2$, $Cu(OTf)_2$ or $Zn(OTf)_2$ resulted in decomposition of **4** and incomplete reaction. Although the diastereoselectivity for this dipolar cycloaddition was moderate, the desired isomer was separated easily from the diastereomeric mixture by recrystalization or flash chromatography. The absolute stereochemistry of the major product **6** (when R=cyclopropyl and R′=phenyl) was determined by X-ray single crystallography.[8] This compound possesses a (3*R*,4*R*) configuration on the pyrrolidine ring as shown by structure **6**.

Conversion of **6** (when R=cyclopropyl, R′=phenyl) to the desired pyrrolidine **9** is efficient and straightforward (Scheme 1). Hydrolysis of **6** with lithium hydroperoxide (LiOH, H_2O_2)[7a] resulted in formation of β-aminoacid **7** and the recovery of chiral auxiliary **2** in nearly quantitative yield. Curtius rearrangement of **7** with diphenylphosphoryl azide (DPPA) in the presence of *t*-BuOH[9] gave BOC-protected aminopyrrolidine **8** in 80% yield. Finally debenzylation under transfer hydrogenation conditions (10% Pd–C, HCO_2NH_4)[10] provided chiral pyrrolidine **9** in quantitative yield. We have applied this synthetic route to construct a series of optically active *trans*-3-amino-4-alkylpyrrolidines for SAR study with overall yields of 46 to 75%. This procedure has also been used for large scale synthesis with the 1,3-dipolar cycloaddition being carried out successfully on more than a 300 gram scale.

In conclusion, we have demonstrated that asymmetric 1,3-dipolar cycloadditions between chiral α,β-unsaturated *N*-acyloxazolidinones and azomethine ylides provide optically active pyrrolidines in excellent yields and moderate diastereoselectivities. Further manipulation of the functional groups led to a series of useful chiral intermediates for the synthesis of the 2-pyridone antibacterial agents.

Table 1. Results of 1,3-dipolar cycloaddition of **3** and **4**



Entry	R	R'	Solvent	Ratio **6**:**5** (a)	Yield(b)
1	Me	i-Pr	CH_2Cl_2	56:44	93 %
2	Me	i-Pr	Toluene	60:40	99 %
3	Me	Bn	Toluene	58:42	88 %
4	Me	Ph	Toluene	73:27	91 %
5	Et	Ph	CH_2Cl_2	57:43	97 %
6	Et	Ph	Toluene	77:33	99 %
7	c-Pr	Ph	CH_2Cl_2	64:36	98 %
8	c-Pr	Ph	Toluene	80:20	99 %
9	Ph	Ph	Toluene	67:33	95 %

(a) ratio determined by NMR integration. (b) isolated yield of diastereomers.

Experimental

General procedure

Melting points were recorded on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured at 20 °C with a Perkin–Elmer 241 polarimeter. Flash column chromatography was carried out on silica gel (230–400 mesh) obtained from EM.

(E)-3-Cyclopropylpropenoic acid (1)

Cyclopropanecarboxaldehyde (50 g, 0.71 mol), malonic acid (78 g, 0.75 mol) and pyridine (80 mL, 994 mol) were heated for 6 hours at 100 °C under N_2. The cooled mixture was acidified with 10% H_2SO_4 (600 mL) and cooled in an ice-bath. The precipitate was collected and washed with water to give **1** as colorless needles (54.9 g, 69% yield): m.p. 66–67 °C (lit.[11] 66.5–67.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (dd, 1H, J=15.0, 10.5 Hz), 5.89 (d, 1H, J=15.0 Hz), 1.61 (m, 1H), 0.98 (m, 2H), 0.58 (m, 2H); MS m/z 130 $(M+NH_4)^+$.

3-[(E)-3-Cyclopropylpropenoyl]-4-(S)-phenyl-2-oxazolidinone (3)

A solution of (*E*)-3-cyclopropylpropenoic acid (**1**, 30.91 g, 0.276 mol) in toluene (400 mL) was cooled to 0 °C under N_2. Oxalyl chloride (70.06 g, 0.552 mol) was added dropwise over 20 minutes with stirring followed by a small amount of anhydrous DMF (0.200 mL). The mixture was stirred at 0 °C for 1 hour and at room temperature for an additional 3 hours. The volatiles were removed under reduced pressure to give the desired acid chloride which was used without further purification.

To a stirred solution of (*S*)-(−)-4-phenyl-2-oxazolidinone (**2**, 39.12 g, 0.240 mol) in THF (600 mL) at −78 °C, was added n-butyllithium (2.5 M in THF, 96.0 mL, 0.240 mol) over 25 minutes under N_2. The crude acid chloride (0.276 mol) was then introduced while maintaining the temperature at −78 °C. The mixture was stirred at this temperature for 30 minutes and allowed to warm to room temperature. Saturated aqueous NH_4Cl solution (150 mL) was added and the THF was removed under reduced pressure. The residue was taken up in ethyl acetate, washed with water, 5% aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. The solvent was evaporated to afford a white solid. The crude product was recrystallized from ethyl acetate and hexane to give **3** as colorless crystals (54.7 g, 89% yield): m.p.

102–103 °C; $[\alpha]_D^{20}$ +163 (c=0.0045, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.42 (m, 6H), 6.54 (dd, 1H, J=15.0, 10.8 Hz), 5.43 (dd, 1H, J=9.0, 3.9 Hz), 4.69 (dd, 1H, J=9.0, 9.0 Hz), 4.17 (dd, 1H, J=9.0, 3.9 Hz), 1.69 (m, 1H), 0.98 (m, 2H), 0.66 (m, 2H); MS m/z 258 $(M+H)^+$, 275 $(M+NH_4)^+$. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.15; H, 5.79; N, 5.46.

1-Benzyl-4-(*R*)-cyclopropyl-3-(*R*)-[(4′-(*S*)-phenyl-2′-oxazolidinon-3′-yl)carbonyl]pyrrolidine (6)

N-Benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine[4a] (**4**, 56.88 g, 0.240 mol) was added to a solution of oxazolidinone **3** (51.40 g, 0.200 mol) in toluene (800 mL) at 0 °C under N_2 and stirred at this temperature for 20 minutes. A solution of trifluoroacetic acid in CH_2Cl_2 (1 M, 20.0 mL, 0.020 mol) was added over 20 minutes with stirring. After being stirred at room temperature for 6 hours, the mixture was washed with 5% aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. The crude product obtained upon evaporation was recrystallized from ethyl acetate and hexane to give the (3*R*,4*R*)-pyrrolidine **6** (30.54 g) as colorless crystals. The filtrate was concentrated and separated by flash column chromatography (silica gel eluting with a gradient of 1:1:2 methylene chloride:ethyl acetate:hexane to 1:1 ethyl acetate:hexane) to give (3*R*,4*R*)-pyrrolidine **6** (30.67 g) and (3*S*,4*S*)-pyrrolidine **5** (15.63 g).

The combined (3*R*,4*R*) isomer **6** (61.21 g, 80%): m.p. 144–145 °C; $[\alpha]_D^{20}$ +103 (c=0.0062, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 10H), 5.43 (dd, 1H, J=9.0, 4.5 Hz), 4.69 (t, 1H, J=9.3 Hz), 4.23 (dd, 1H, J=9.0, 4.5 Hz), 3.98 (m, 1H), 3.65 (d, 1H, J=13.5 Hz), 3.44 (d, 1H, J=13.5 Hz), 3.03 (dd, 1H, J=9.3, 9.0 Hz), 2.84 (dd, 1H, J=9.0, 8.4 Hz), 2.64 (dd, 1H, J=10.2, 6.0 Hz), 2.36 (dd, 1H, J=9.0, 5.2 Hz), 2.08 (m, 1H), 0.77 (m, 1H), 0.40 (m, 2H), 0.09 (m, 1H); MS m/z 391 $(M+H)^+$. Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.90; H, 6.57; N, 7.17.

The (3*S*,4*S*) isomer **5** (15.63 g, 20%): m.p. 115–116 °C; $[\alpha]_D^{20}$ +56 (c=0.0044, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 10H), 5.42 (dd, 1H, J=9.0, 4.5 Hz), 4.66 (t, 1H, J=9.0 Hz), 4.26 (dd, 1H, J=9.0, 4.5 Hz), 4.10 (m, 1H), 3.66 (d, 1H, J=12.9 Hz), 3.55 (d, 1H, J=12.9 Hz), 3.01 (dd, 1H, J=9.3, 9.0 Hz), 2.87 (dd, 1H, J=9.0, 8.4 Hz), 2.69 (dd, 1H, J=9.6, 6.3 Hz), 2.41 (dd, 1H, J=9.0, 7.8 Hz), 1.90 (m, 1H), 0.75 (m, 1H), 0.34 (m, 1H), 0.25 (m, 1H), −0.02 (m, 1H); MS m/z 391 $(M+H)^+$. Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.89; H, 6.62; N, 7.21.

*(3*R*,4*R*)-1-Benzyl-4-cyclopropyl-3-carboxypyrrolidine (7)*

A solution of LiOH (15.75 g, 0.375 mol) and H_2O_2 (30%, 34.00 mL, 0.300 mol) in water (200 mL) was added to a stirred solution of pyrrolidine **6** (58.50 g, 0.150 mol) in THF (600 mL) at 0 °C over 30 minutes. The mixture was stirred at this temperature for 1 hour, then diluted with water (800 mL). Sodium sulfite (37.8 g, 0.300 mol) was added and the mixture was extracted with ethyl acetate. The aqueous phase was adjusted to pH 4.6 with NaH_2PO_4 (68 g, 0.50 mol) and 10% HCl, then saturated with NaCl (200 g). This solution was extracted with isopropyl alcohol:methylene chloride (1:3), which was washed with brine, dried over Na_2SO_4 and evaporated to afford **7** as a white solid (37.0 g, 100%): ^1H NMR (300 MHz, $CDCl_3$) δ 11.55 (br. s, 1H), 7.60 (m, 2H), 7.39 (m, 3H), 4.32 (AB q, 2H), 3.61 (m, 2H), 3.43 (m, 1H), 3.18 (m, 1H), 3.14 (m, 1H), 2.05 (m, 1H), 0.91 (m, 1H), 0.45 (m, 1H), 0.31 (m, 1H), 0.10 (m, 1H); MS m/z 246 $(M+H)^+$.

*(3*R*,4*R*)-1-Benzyl-4-cyclopropyl-3-(*tert*-butoxycarbonyl)aminopyrrolidine (8)*

Carboxypyrrolidine **7** (37.00 g, 0.150 mol) was dissolved in *t*-butanol, and the solution was flushed with N_2. Triethylamine (30.35 g, 0.300 mol) and diphenylphosphoryl azide (47.47 g, 0.173 mol) were added via syringe. The mixture was heated to 95 °C for 72 hours. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel to afford **8** as a yellow oil (37.86 g, 80%): $[\alpha]_D^{20}$ +10 (c=0.0051, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 5H), 4.00 (m, 1H), 3.64 (m, 2H), 3.05 (m, 1H), 2.73 (m, 2H), 2.16 (m, 1H), 1.44 (s, 9H), 1.21 (m, 1H), 0.72 (m, 1H), 0.45 (m, 2H), 0.22 (m, 1H), 0.06 (m, 1H); MS m/z 317 $(M+H)^+$. HRMS Calcd for $C_{19}H_{29}N_2O_2$ $(M+H)^+$: 317.2229. Found: 317.2220.

*(3R,4R)-4-Cyclopropyl-3-(*tert*-butoxycarbonyl)aminopyrrolidine (9)*

Ammonium formate (36.0 g, 0.570 mol) and 10% Pd–C (1.6 g) were added to a solution of pyrrolidine **8** (37.8 g, 0.105 mol) in methanol under N_2. The mixture was heated at 80 °C for 5 hours, cooled, diluted with methylene chloride, filtered and concentrated to give **9** as a colorless oil (23.0 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (1H, m), 3.38 (2H, m), 3.14 (1H, m), 2.94 (1H, m), 1.22 (1H, m), 1.43 (9H, s), 0.65 (1H, m), 0.53 (2H, m), 0.33 (1H, m), 0.14 (1H, m): MS m/z 227 $(M+H)^+$.

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