Stereoselective Synthesis of Substituted Pyrrolidines by a Domino Michael Addition/Carbocyclization Reaction

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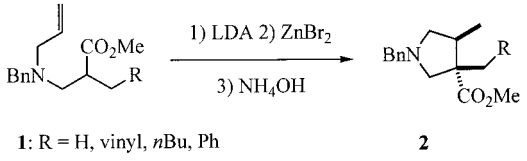
Dedicated to Marc Julia on the occasion of his 80th birthday

Keywords: Michael addition / Cyclization / Copper / Zinc / Domino reactions / Nitrogen heterocycles

The domino 1,4-addition/carbocyclization/functionalization reaction of Michael acceptor **3** with mixed copper/zinc reagents allows the totally diastereoselective formation of 3,4-disubstituted-3-carbomethoxypyrrolidines in a three-component one-pot sequence.

Introduction

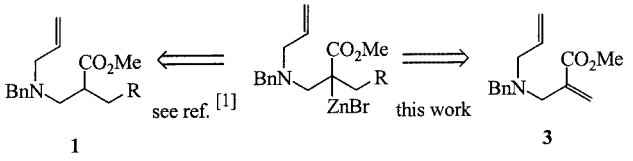
We have recently shown[1] that zinc enolates derived from substituted β-(*N*-allyl)-amino esters **1** undergo a smooth carbocyclization reaction to give 3,4-disubstituted-3-carbomethoxypyrrolidines **2** with excellent stereochemical control (Scheme 1).



1: R = H, vinyl, *n*Bu, Ph **2**

Scheme 1

These zinc enolates were prepared by deprotonation of the corresponding esters with LDA and subsequent transmetalation with zinc salts. However, in some cases we observed a β-elimination side reaction due presumably to the instability of the lithium enolate in the presence of zinc salts. In order to avoid this side reaction, we decided to prepare these Reformatsky reagents by 1,4-addition of organometallic reagents onto the appropriate Michael acceptor **3** (Scheme 2).



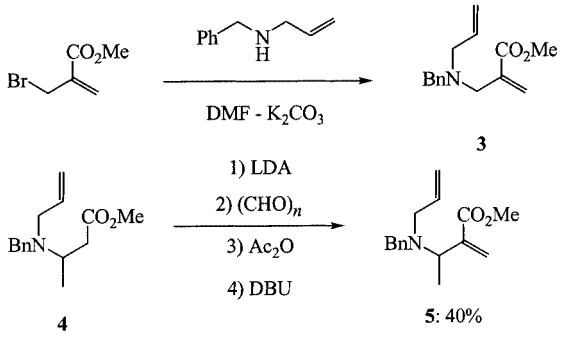
1 **3**

Scheme 2

Results and Discussion

Preparation of Starting Materials

The Michael acceptor **3** was prepared by reaction of commercially available methyl 2-(bromomethyl)acrylate with *N*-allyl-*N*-benzylamine (Scheme 3). Compound **5** was prepared from the corresponding β-amino ester **4** by the three-step procedure depicted in Scheme 3 in 40% overall yield.



Scheme 3

Reaction of 3 and 4 with Triorganozincates and Organocopper Reagents

Triorganozincate reagents[2] are known to undergo a 1,4-addition with enones,[3−10] although to the best of our knowledge, few examples concern the reaction with α,β-un-

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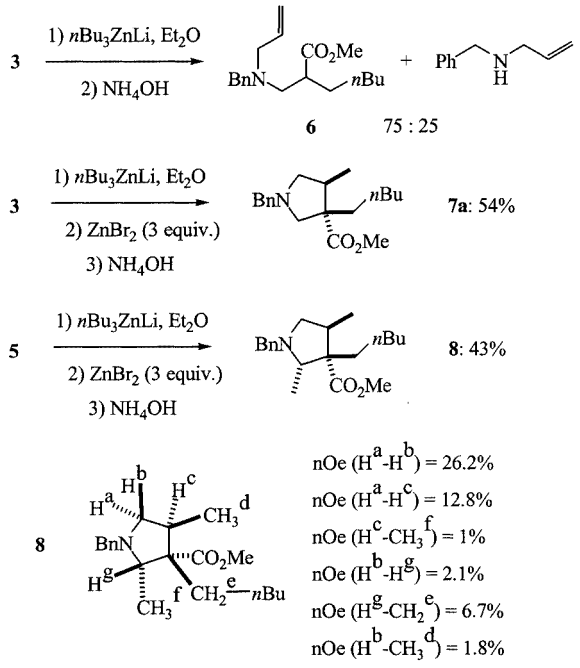
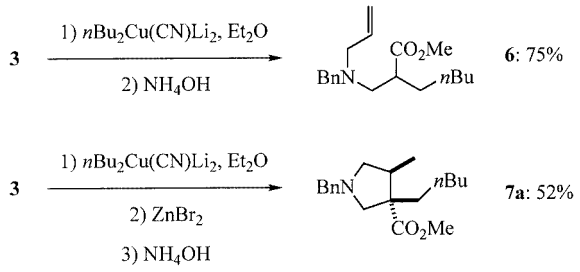
saturated esters.[11,12] The reaction of lithium tri-*n*-butylzincate with compound **3** at 0 °C in diethyl ether gives, after hydrolysis, the 1,4-addition product **6** in 75% yield accompanied by 25% of *N*-allyl-*N*-benzylamine resulting from a β-elimination reaction (Scheme 4). On the other hand, the addition of zinc bromide after completion of the Michael addition promotes the carbocyclization of the resulting enolate efficiently to give, after hydrolysis, the carbomethoxypyrrolidine **7a** in a 54% isolated yield and as a single diastereomer. This diastereomer was found to be identical to the one obtained by deprotonation [1] of the corresponding substituted β-(*N*-allyl)amino ester (Scheme 4).



Scheme 4

The same domino 1,4-addition/carbocyclization reaction was performed with the substituted enoate **5**. In this case, the carbomethoxypyrrolidine **8** was obtained as a mixture of two diastereomers in an 85:15 ratio. The relative configurations for the major diastereomer, isolated in a 43% yield, were determined on the basis of nuclear Overhauser effects (Scheme 4).

Reaction of **3** with *n*BuCu/LiI and the cyanocuprate reagent *n*BuCu(CN)Li, when conducted in diethyl ether, gave only products from the β-elimination process. This elimination process has already been observed in some similar 1,4-additions of organocopper reagents to 2-(methylamino)-enones.[13] On the other hand, the reaction of the higher order cyanocuprate $nBu_2Cu(CN)Li_2$ gave the 1,4-addition product **6** in 75% isolated yield upon hydrolysis, accompanied by *N*-allyl-*N*-benzylamine (20%). Here again, the enolate resulting from the Michael addition underwent carbocyclization reaction only upon addition of zinc bromide, and the resulting carbomethoxypyrrolidine **7a** was obtained in a 52% isolated yield and as a single diastereomer (Scheme 5).

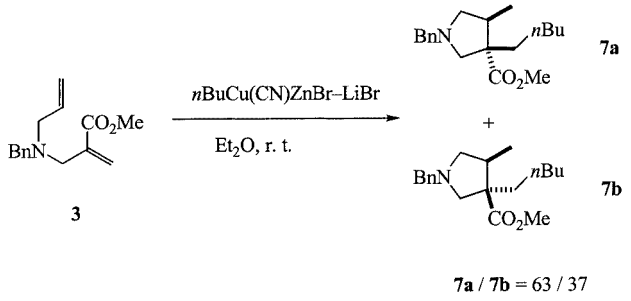


Scheme 5

These encouraging results led us to examine other organometallic species in order to avoid any excess of carbanionic ligand. As zinc salts are required for the carbocyclization reaction, we turned to mixed organocopper/zinc reagents.[14]

Domino 1,4-Addition/Carbocyclization Reaction with Mixed Organocopper/Zinc Reagents

To the best of our knowledge, the only examples of 1,4-addition of these reagents to α,β-ethylenic esters reported in the literature are conducted in polar solvents with TMSCl activation.[15] However, we were pleased to see that the reaction of *n*BuCu(CN)ZnBr/LiBr (prepared from *n*BuLi and a mixture of $ZnBr_2$ and CuCN in diethyl ether) gave the cyclized product **7** smoothly in good yield, albeit with a moderate stereoselectivity (**7a**/**7b** = 63:37, Scheme 6). No intermediate product (namely **6** upon hydrolysis) could be detected, nor could any elimination product. In order to improve the stereoselectivity, we tried to modify the reaction conditions (temperature, $ZnBr_2$ or CuCN equivalents, additives...). These results are reported in Table 1. In all cases, crude **7** was obtained in 75−85% yield and the ratio of **7a** to **7b** determined by GC analysis.



Scheme 6

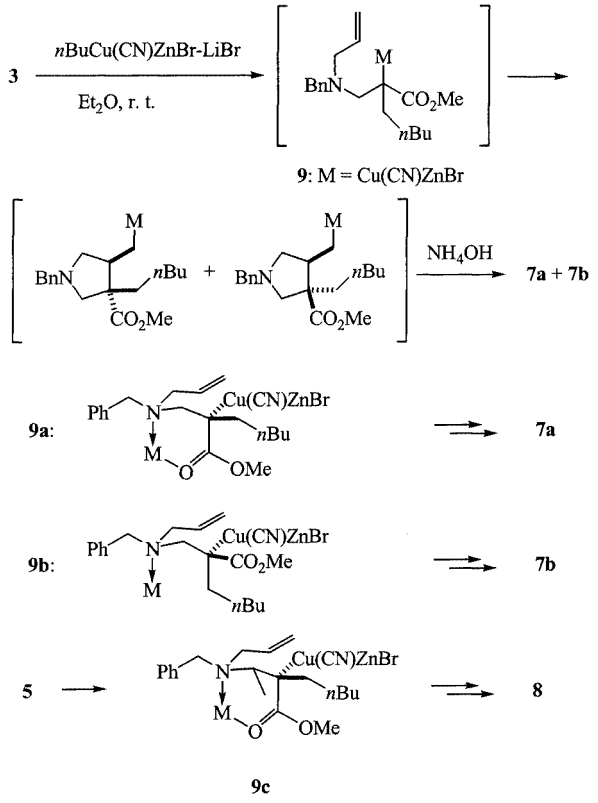
The diastereoselectivity of this domino reaction is of course determined in the second step, namely the carbocyclization reaction. We can assume that the enolate obtained after the Michael reaction is a copper/zinc mixed enolate. The stereoselectivity of the carbocyclization reaction of zinc enolates prepared by deprotonation and subsequent transmetalation was interpreted in terms of the reaction of a carbon-centered zinc enolate.[1] The stereoselectivity here

Table 1. Domino 1,4-addition/carbocyclization on **3** with *n*BuCu(CN)ZnBr·LiBr

Entry	CuCN	$ZnBr_2$	Additives	Temperature	**7a/7b** ratio[a]
1	1 equiv.	1 equiv.	-	room temp.	63:37
2	1	2	-	room temp.	90:10
3	1	3	-	room temp.	93:7
4	1	1	LiBr (1equiv.)	room temp.	63:37
5	1	1	LiBr (2 equiv.)	room temp.	47:53
6	1	1	$MgBr_2$ (1 equiv.)	room temp.	77:33[b]
7	0.1	1	-	room temp.	52:48
8	2	1	-	room temp.	43:57
9	1	1	-	room temp.	84:16[c]
10	1	1	-	−20 °C	80:20[c]

[a] Determined by GC analysis. [b] Accompanied by 20% of *N*-benzyl-*N*-allylamine (by GC). [c] With two equivalents of *n*BuCu(CN)ZnBr/LiBr.

can also be interpreted with the intermediacy of carbon-centred copper/zinc enolates **9a** and **9b**, which should show the same reactivity and stereoselectivity trends, as depicted in Scheme 7. The substituted enolate derived from the 1,4-addition to **5** should cyclize through the carbon-centered copper/zinc enolate **9c**, which has the methyl group in a pseudoequatorial position, to give compound **8** as a major product.

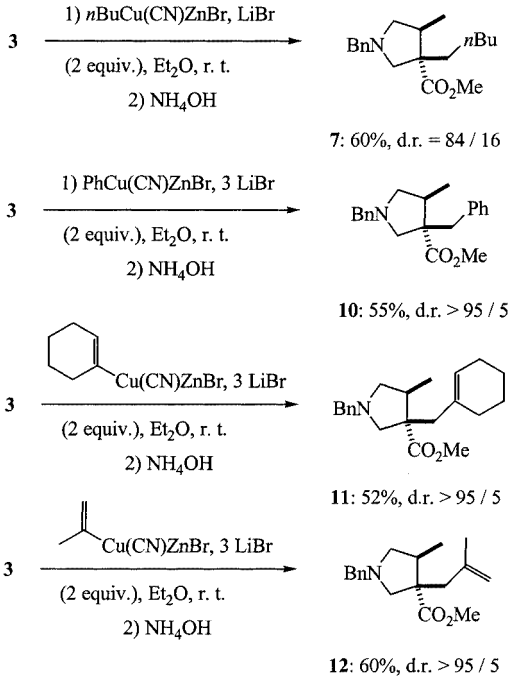


Scheme 7

In such an interpretation, and with the highly probable hypothesis of a high configurational instability of enolates **9a** and **9b**,[16] cyclization through enolate **9a** should be favoured over cyclization through enolate **9b** on the basis of simple steric hindrance. Intermediate **9a** should be even more favoured in the presence of an excess of Lewis acid such as $MgBr_2$ or $ZnBr_2$, as shown in Table 1 (entries 2,3 and 6). On the other hand, the influence of an excess of lithium salts (Table 1, entry 5) as well as the influence of an excess or a deficit of copper salt (entries 7 and 8) are more difficult to interpret; however, in these cases, the nature of the enolate could be changed. Finally, for as yet unknown reasons, the diastereoselectivity is better when an excess of mixed organocopper/zinc reagent is used (Table 1, entry 9), and is not sensitive to temperature (Table 1, entry 10 versus 9). It should be noted that all reactions were complete within two hours.

Domino Michael Addition/Carbocyclization Reaction with Other Mixed Copper/Zinc Reagents

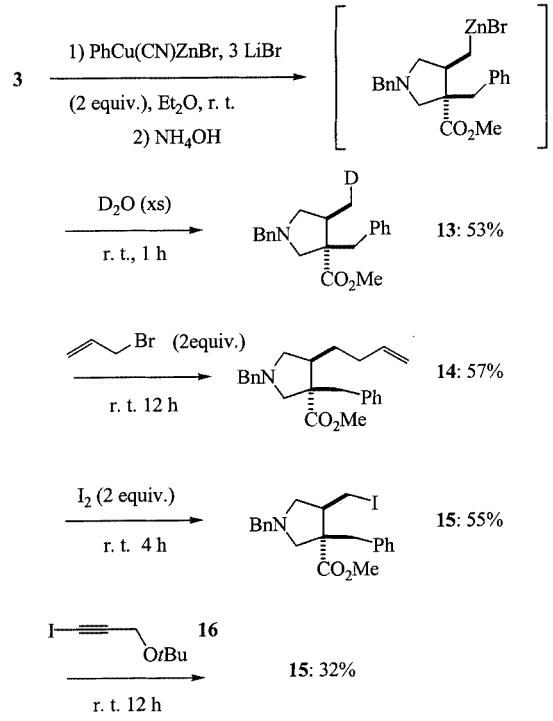
We examined our domino reaction with various other copper/zinc species. We were very pleased to see that the diastereoselectivity was totally controlled by using aryl or vinylic organometallic reagents as can be seen in Scheme 8. Surprisingly, these species, when made from "salt-free" or "non salt-free" organolithium reagents, gave the same excellent diastereoselectivity, as only one diastereomer for **10**, **11** and **12** was evidenced by ^1H NMR spectroscopy. This is the reverse to what was observed in the case of alkyllithium reagents (see Table 1, entries 1,4 and 5). Here again, the nature of the intermediate enolate could be different, depending on the nature of the substituent introduced during the 1,4-addition reaction.



Scheme 8

Reaction of the Resulting Pyrrolidinylmethylzinc Reagent with Electrophiles

We have already shown in our previous work that pyrrolidinylmethylzinc reagents derived from the carbocyclization of zinc enolates can be functionalized with various electrophiles. In some cases, CuCN addition was necessary to enhance the reactivity of the zinc reagent. In the present case, however, a copper salt is already present in the reaction mixture, and we wanted to verify that, as in the previous example, the resulting organometallic reagent could be widely functionalized. The formation of the pyrrolidinylmethylzinc, or -copper/zinc, reagent resulting from the domino 1,4-addition/carbocyclization reaction with PhCu(CN)-ZnBr·3LiBr was confirmed by its reactions with various electrophiles, as depicted in Scheme 9. In each case, the diastereoselectivity was excellent, as only one diastereomer was seen by ^{1}H NMR spectroscopy. The yields reported in Scheme 9 are isolated yields after purification.



Scheme 9

Reaction of the pyrrolidinylmethyl organometallic reagent with deuterium oxide gave the deuterated pyrrolidine **13** in 57% yield as a single diastereomer. Coupling with allyl bromide gave the pyrrolidine **14** in 57% yield, and reaction with iodine gave the iodopyrrolidine **15** in 55% isolated yield. It should be noted that in this type of functionalization, three carbon-carbon bonds are formed in a one-pot procedure. Surprisingly, the reaction with iodoalkyne **16** gave only the iodopyrrolidine **15** in 32% yield and not the expected coupled pyrrolidinylalkyne. This non-classical behaviour is still unexplained; however, it could be a sign that the organometallic reagent resulting from the domino 1,4-addition/carbocyclization reaction is a true organozinc compound, and not a mixed copper-zinc reagent, as these reagents are known to undergo a smooth coupling reaction with iodoalkynes.[17]

Conclusion

We have disclosed a domino 1,4-addition/carbocyclization reaction with electrophiles that allows the totally stereoselective construction of various 3,4-disubstituted-3-carbomethoxypyrrolidines, with the concomitant formation of two or three carbon-carbon bonds in a two- or three-step one-pot procedure. The organometallic reagents involved in this domino reaction can either be zincates, higher order cyanocuprates or mixed copper/zinc compounds. This interesting methodology leads with a great versatility to substituted β-proline-type heterocycles, compounds with a great synthetic potential and biological interest.[18]

Experimental Section

General Remarks: Experiments involving organometallic reagents were carried out in dry glassware under a positive pressure of dry nitrogen. Liquid nitrogen was used as a cryoscopic fluid. A four-necked round-bottomed flask equipped with an internal thermometer, a septum cap, a nitrogen inlet and a mechanical stirrer was used. THF was freshly distilled from sodium/benzophenone ketyl prior to use. Zinc bromide (98%) was purchased from Aldrich. It was melted under dry nitrogen and, immediately after cooling down to room temperature, was dissolved in anhydrous THF. All other reagents and solvents were of commercial quality and were used without purification. Flash column chromatographic separations were carried out over Merck silica gel 60 (0.015−0.040 mm). ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX 400 or AC 200 spectrometers. Chemical shifts are reported relative to an internal standard of residual chloroform (δ = 7.27 ppm for ^{1}H and δ = 77.1 ppm for ^{13}C) unless otherwise noted. IR spectra were recorded with a Perkin−Elmer 1420 spectrophotometer. Mass spectra were performed by the Service de Spectrométrie de Masse de l'Université Pierre et Marie Curie. Elemental analyses were performed by the Service de Microanalyses de l'Université Pierre et Marie Curie.

Methyl 2-[(*N*-Allyl-*N*-benzylamino)methyl]acrylate (3): K_2CO_3 (6.90 g, 50 mmol) and NaI (0.75 g, 5 mmol) were added to a stirred solution of *N*-allyl-*N*-benzylamine (7.35 g, 50 mmol) in DMF (50 mL). The mixture was cooled to −10 °C and a solution of methyl (bromomethyl)acrylate (8.95 g, 50 mmol) in DMF (50 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with brine (100 mL), Et_2O (50 mL) was added and the layers were separated, the aqueous one being extracted three times with Et_2O. The combined organic layers were washed six times with brine, dried over $MgSO_4$, the solvents evaporated under reduced pressure and the residue purified by chromatography with cyclohexane/EtOAc (80:20) as eluent to give **3** (10.79 g, 88%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3063, 2949, 2926, 2799, 1721, 1636, 1494, 1438, 1386, 1307, 1262, 1195, 1154, 1119, 983, 921, 818, 740, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10 (d, *J* = 6.11 Hz, 2 H), 3.33 (s, 2 H), 3.63 (s, 2 H), 3.75 (s, 3 H), 5.17 (dd, *J* = 10.2, 1.5 Hz, 1 H), 5.23 (dd, *J* = 17.3, 1.5 Hz, 1 H), 5.90 (ddt, *J* = 17.3, 10.2, 6.6 Hz,

1 H,), 5.95 (d, J = 1.5 Hz, 1 H), 6.30 (d, J = 1.5 Hz, 1 H), 7.23−7.36 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.68, 53.85, 56.60, 58.03, 117.32, 125.95, 126.90, 128.24 (2C), 128.62 (2C), 135.74, 138.39, 139.48, 167.47 ppm. $C_{15}H_{19}NO_2$ (245.3206): calcd. C 73.44; H 7.81; N 5.71; found C 73.35; H 7.96; N 5.71.

Methyl 3-(*N*-Allyl-*N*-benzylamino)butyrate (4): Methyl crotonate (40 g, 400 mmol) was added at room temperature to a stirred solution of benzylamine (21.6 g, 200 mmol) in MeOH. After stirring at room temperature for 72 h, the solvent and the excess of methyl crotonate were removed under reduced pressure. Crude methyl 3-(*N*-benzylamino)butyrate (40.62 g, 98%) was used for further transformation without purification. IR (neat): $\tilde{\nu}$ = 3600−3200, 3027, 2950, 2933, 2862, 1736, 1661, 1494, 1453, 1437, 1376, 1295, 1254, 1195, 1175, 1028, 1009, 737, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, J = 6.6 Hz, 3 H), 1.60−1.92 (1 H), 2.39 (dd, J = 15.3, 5.6 Hz, 1 H), 2.50 (dd, J = 15.3, 6.6 Hz, 1 H), 3.16 (sext, J = 6.6 Hz, 1 H), 3.67 (s, 3 H), 3.76 (d, J = 13.2 Hz, 1 H), 3.83 (d, J = 13.2 Hz, 1 H), 7.22−7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.58, 41.53, 49.76, 51.30, 51.64, 127.05, 128.22 (2C), 128.54 (2C), 140.45, 172.91.

K_2CO_3 (120 mmol) and a solution of allyl bromide (9.6 mL, 110 mmol) in DMF (40 mL) at 0 °C were added to a stirred solution of methyl 3-(*N*-benzylamino)butyrate (20.8 g, 100 mmol) in DMF (100 mL). The cold bath was removed and the solution was allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 12 h and hydrolysed with an aqueous saturated solution of $NaHCO_3$ (200 mL). Et_2O (100 mL) was added and the layers separated, the aqueous one being extracted three times with Et_2O. The combined organic layers were washed ten times with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by chromatography with cyclohexane/ethyl acetate (90:10) as eluent to give **4** (22.7 g, 92%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3064, 3026, 2950, 2933, 2878, 2806, 1739, 1494, 1453, 1436, 1372, 1297, 1257, 1198, 1156, 1073, 1028, 996, 918, 740, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, J = 6.8 Hz, 3 H), 2.29 (dd, J = 14.1, 7.1 Hz, 1 H), 2.60 (dd, J = 14.1, 7.8 Hz, 1 H), 2.97 (dd, J = 14.2, 7.2 Hz, 1 H), 3.14 (dd, J = 14.2, 5.2 Hz, 1 H), 3.36−3.47 (m, 1 H), 3.44 (d, J = 13.9 Hz, 1 H), 3.65 (s, 3 H), 3.69 (d, J = 13.9 Hz, 1 H), 5.07−5.12 (m, 1 H), 5.15−5.22 (m, 1 H), 5.75−5.86 (m, 1 H), 7.21−7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.90, 39.09, 51.22, 51.31, 52.48, 52.99, 116.43, 126.65, 127.99 (2C), 128.46 (2C), 137.08, 140.03, 172.56.

Methyl 2-[1-(*N*-Allyl-*N*-benzylamino)ethyl]acrylate (5): *n*BuLi (24.8 mL, 2.5 in hexanes, 62 mmol) was added to a stirred solution of diisopropylamine (8.8 mL, 62.6 mmol) in THF (30 mL) at −70 °C. After stirring at −70 °C for 30 min and then at 0 °C for an additional 30 min, the solution was cooled to −78 °C and a solution of **4** (7.67 g, 31 mmol) in THF (50 mL) was added dropwise at −78 °C. This mixture was stirred at −78 °C for 1 h. Paraformaldehyde (2.7 g, 90 mmol) was then added in one portion at −78 °C, the cold bath removed and the reaction mixture stirred at room temperature for 30 min. The solution was hydrolysed with a saturated aqueous solution of $NaHCO_3$. Et_2O (30 mL) was added and the layers were separated, the aqueous one being extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure.

The crude material was diluted with CH_2Cl_2 (120 mL) under argon atmosphere. Pyridine (2.8 mL, 34 mmol) and Ac_2O (3.5 mL, 37 mmol) were added at room temperature. The mixture was stirred at room temperature for 12 hours and hydrolysed with a saturated aqueous solution of NH_4Cl/NH_3. The layers were separated, the aqueous one being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure.

The crude material was diluted with CH_2Cl_2 (100 mL) and DBU (13.7 g, 90 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 4 days. The solvents were evaporated under reduced pressure and the residue diluted in Et_2O (50 mL). A saturated aqueous solution of $NaHCO_3$ (50 mL) was added and the layers were separated, the aqueous one being extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The residue was purified by chromatography using cyclohexane as eluent to give **5** (3.22 g, 40%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3063, 3027, 2973, 2927, 2804, 1723, 1642, 1494, 1436, 1374, 1276, 1155, 1062, 994, 919, 740, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, J = 6.6 Hz, 3 H), 2.96 (dd, J = 14.2, 7.6 Hz, 1 H), 3.15 (ddt, J = 14.2, 5.1, 1.5 Hz, 1 H), 3.35 (d, J = 14.2 Hz, 1 H), 3.70 (d, J = 14.2 Hz, 1 H), 3.74 (s, 3 H), 4.00 (q, J = 6.6 Hz, 1 H), 5.07−5.09 (m, 1 H), 5.14 (dq, J = 17.3, 1.5 Hz, 1 H), 5.58 (s, 1 H), 5.83 (m, 1 H), 6.07 (s, 1 H), 7.16−7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.22, 51.68, 52.85, 53.08, 53.48, 116.61, 122.56, 126.72, 128.12 (2C), 128.62 (2C), 137.01, 140.31, 144.38, 168.70 ppm. $C_{16}H_{21}NO_2$ (259.34): calcd. C 74.10, H 8.16, N 5.40; found C 73.94, H 8.24, N 5.27.

General Procedure A: Cyclisation with Zincates: *n*BuLi (3.6 mL, 2.5 in hexanes, 9 mmol) was added dropwise to a solution of zinc bromide (3 mL, 1 N in Et_2O, 3 mmol) at −80 °C diluted with 10 mL Et_2O. The cold bath was removed and the temperature was allowed to reach 0 °C. After 15 min at 0 °C, the mixture was cooled to −78 °C and a solution of ester **3** or **5** (2 mmol) in Et_2O (5 mL) was added dropwise. The mixture was stirred at −78 °C for 1 hour and then allowed to warm to 0 °C. A solution of zinc bromide (9 mL, 1 N in Et_2O, 9 mmol) was added at 0 °C and the cold bath removed. After being stirred for 30 min at room temperature, the reaction was hydrolysed with an aqueous solution of NH_4Cl/NH_4OH (2:1). The layers were separated, the aqueous one being extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure.

General Procedure B: Conjugate Addition/Cyclization of Zinc/Copper Reagents: An ethereal solution of zinc bromide (4 mL, 1 N in Et_2O, 4 mmol) and a solution of RLi (4 mmol in Et_2O) were added dropwise consecutively to a suspension of copper cyanide (360 mg, 4 mmol) in Et_2O (7 mL) at −10 °C. The reaction mixture was stirred at 0 °C for 1 h and a solution of **3** (2 mmol) in Et_2O was added dropwise at 0 °C. The cold bath was removed and the biphasic mixture was stirred at room temperature for 2 h. The reaction was hydrolysed with an aqueous solution of NH_4Cl/NH_4OH (2:1). The layers were separated, the aqueous one being extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents evaporated under reduced pressure.

Methyl (3*S,4*S**)-1-Benzyl-4-methyl-3-pentylpyrrolidine-3-carboxylate (7a):** Prepared according to procedure A from **3** (490 mg, 2 mmol). The residue was chromatographed with cyclohexane/EtOAc (80:20) as eluent to give **7a** (267 mg, 54%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3027, 2953, 2932, 2861, 2788, 1732, 1495, 1454, 1378, 1290, 1256, 1196, 1138, 1072, 1029, 738, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.1 Hz, 3 H), 0.93−1.13 (m, 2 H), 0.99 (d, J = 7.1 Hz, 3 H), 1.16−1.27 (m, 4 H), 1.31−1.39 (m, 1 H), 1.62−1.71 (m, 1 H), 1.98 (t, J = 8.64 Hz, 1 H), 2.08 (d,

J = 9.7 Hz, 1 H), 2.41−2.51 (m, 1 H), 2.91−2.97 (m, 1 H), 3.44 (d, J = 9.7 Hz, 1 H), 3.51 (d, J = 13.7 Hz, 1 H), 3.62 (d, J = 13.7 Hz, 1 H), 3.65 (s, 3 H), 7.18−7.31 (m, 5 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.91, 14.07, 22.54, 25.28, 32.44, 33.10, 39.80, 51.84, 54.53, 60.28, 61.55, 61.70, 126.87, 128.25 (2C), 128.61 (2C), 139.31, 177.39 ppm. $C_{19}H_{29}NO_2$ (303.4958): calcd. C 75.21, H 9.63, N 4.62; found C 75.04, H 9.64, N 4.49.

Methyl (2*S,3*S**,4*S**)-1-Benzyl-2,4-dimethyl-3-pentylpyrrolidine-3-carboxylate (8):** Prepared according to Procedure A from **5** (634 mg, 1 mmol) to yield the corresponding pyrrolidine as a mixture of diastereoisomers in an 85:15 ratio (determined by GC). The residue was chromatographed with cyclohexane/EtOAc (80:20) as eluent to give **8** (368 mg, 58%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3027, 2932, 2871, 1730, 1453, 1228, 1196, 1139, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.9 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H), 1.09 (d, J = 6.3 Hz, 3 H), 1.13−1.37 (m, 6 H), 1.44−1.61 (m, 2 H), 1.96 (dd, J = 9.2, 7.6 Hz, 1 H), 2.61 (q, J = 6.3 Hz, 1 H), 2.74 (sext, J = 7.2 Hz, 1 H), 3.11 (dd, J = 9.2, 7.6 Hz, 1 H), 3.28 (d, J = 13.2 Hz, 1 H), 3.69 (s, 3 H), 3.93 (d, J = 13.2 Hz, 1 H), 7.20−7.35 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.23, 15.22, 15.87, 22.64, 25.21, 32.69, 32.90, 36.39, 51.32, 57.73, 58.37, 59.83, 66.20, 126.84, 128.24 (2C), 128.83 (2C), 139.58, 175.80 ppm. $C_{20}H_{31}NO_2$ (317.47): calcd. C 75.67, H 9.84, N 4.41; found C 75.70, H 9.94, N 4.42.

Methyl (3*R,4*S**)-1,3-Dibenzyl-4-methylpyrrolidine-3-carboxylate (10):** Prepared according to procedure B from **3** (490 mg, 2 mmol) and PhLi·LiBr (3.2 mL, 1.27 N in Et_2O, 4 mmol). The residue was chromatographed with cyclohexane/EtOAc (80:20) as eluent to give **10** (356 mg, 55%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3062, 3028, 2959, 2795, 1728, 1604, 1495, 1473, 1454, 1436, 1377, 1357, 1314, 1271, 1196, 1133, 1097, 1070, 1029, 910, 735, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, J = 7.1 Hz, 3 H), 2.44 (t, J = 8.6 Hz, 1 H), 2.60 (d, J = 9.9 Hz, 1 H), 2.68 (m, 1 H), 2.86 (d, J = 13.4 Hz, 1 H), 3.02 (t, J = 8.6 Hz, 1 H), 3.24 (d, J = 9.9 Hz, 1 H), 3.28 (d, J = 13.4 Hz, 1 H), 3.72 (s, 3 H), 3.74 (s, 2 H), 7.15−7.46 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.06, 38.09, 40.88, 51.78, 55.58, 59.95, 60.27, 60.86, 126.59, 127.05, 128.35 (4C), 128.82 (2C), 129.66 (2C), 138.30, 139.13, 176.42 ppm. $C_{21}H_{25}NO_2$ (323.434): calcd. C 77.98, H 7.79, N 4.33; found C 78.12, H 7.73, N 4.26.

Methyl (3*S,4*S**)-1-Benzyl-3-(cyclohex-1′-enylmethyl)-4-methylpyrrolidine-3-carboxylate (11):** Prepared according to procedure B from **3** (490 mg, 2 mmol) and cyclohexenyllithium (2.26 mL, 1.77 N in Et_2O, 4 mmol). The residue was purified by chromatography with cyclohexane/EtOAc (80:20) as eluent to give **11** (341 mg, 52%) as a pale yellow oil. IR (neat): $\tilde{\nu}$ = 3026, 2932, 2861, 2835, 2791, 1731, 1495, 1453, 1375, 1270, 1202, 1172, 1136, 1099, 1069, 1028, 741, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (d, J = 7.1 Hz, 3 H), 1.43−1.56 (m, 4 H), 1.69−1.82 (m, 2 H), 1.82−1.93 (m, 2 H), 2.06 (d, J = 13.7 Hz, 1 H), 2.09 (t, 1 H, J = 9.2 Hz, 8.6 Hz), 2.31 (d, J = 10.2 Hz, 1 H), 2.43−2.49 (m, 2 H), 2.91 (dd, J = 9.2, 7.6 Hz, 1 H), 3.41 (d, J = 10.2 Hz, 1 H), 3.61 (s, 2 H), 3.66 (s, 3 H), 5.34 (s, 1 H), 7.21−7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.75, 22.24, 23.05, 25.45, 29.01, 40.94, 41.23, 51.74, 53.62, 60.21, 60.78, 61.02, 124.46, 126.80, 128.20 (2C), 128.58 (2C), 134.41, 139.34, 177.30 ppm. HR MS (CI, methane): m/z = $C_{21}H_{30}NO_2$ [MH^+]: calcd. 328.2277; found 328.2271.

Methyl (3*S,4*S**)-1-Benzyl-4-methyl-3-(2-methylallyl)pyrrolidine-3-carboxylate (12):** Prepared according to procedure B from **3** (490 mg, 2 mmol) and isopropenyllithium·LiBr (3.3 mL, 1.22 N in Et_2O, 4 mmol). The residue was chromatographed with cyclohexane/EtOAc (80:20) as eluent to give **12** (345 mg, 60%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3063, 3027, 2933, 2862, 2792, 1731, 1647, 1495, 1453, 1435, 1376, 1356, 1301, 1199, 1136, 1100, 1076, 1028, 893, 740, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, J = 7.3 Hz, 3 H), 1.64 (s, 3 H), 2.13 (t, J = 8.8 Hz, 1 H), 2.19 (d, J = 14.5 Hz, 1 H), 2.36 (d, J = 9.8 Hz, 1 H), 2.47−2.54 (m, 1 H), 2.58 (d, J = 14.5 Hz, 1 H), 2.95 (dd, J = 8.8, 7.3 Hz, 1 H), 3.47 (d, J = 9.8 Hz, 1 H), 3.60 (d, J = 13.2 Hz, 1 H), 3.66 (d, J = 13.2 Hz, 1 H), 3.69 (s, 3 H), 4.64 (s, 1 H), 4.76 (s, 1 H), 7.22−7.25 (m, 1 H), 7.30−7.35 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.68, 23.41, 40.58, 41.03, 51.83, 53.29, 60.17, 60.91, 60.96, 113.31, 126.83, 128.20 (2C), 128.58 (2C), 139.20, 142.41, 177.05 ppm. $C_{18}H_{25}NO_2$ (287.401): calcd. C 75.22, H 8.77, N 4.87; found C 75.10, H 8.89, N 4.78.

Methyl (3*S,4*S**)-4-Deuteromethyl-1,3-dibenzylpyrrolidine-3-carboxylate (13):** Prepared according to procedure B from **3** (491 mg, 2 mmol). The reaction was hydrolysed with D_2O (2 mL) after 24 hours at room temperature. After work up, the residue was chromatographed with cyclohexane/EtOAc (80:20) as eluent to give **13** (344 mg, 53%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3062, 3027, 2933, 2862, 2795, 1729, 1495, 1453, 1194, 1094, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, J = 7.1 Hz, 2 H), 2.33 (t, J = 8.7 Hz, 1 H), 2.47 (d, J = 9.7 Hz, 1 H), 2.55 (quint., J = 7.6 Hz, 1 H), 2.77 (d, J = 13.2 Hz, 1 H), 2.91 (t, J = 8.7 Hz, 1 H), 3.09 (d, J = 9.7 Hz, 1 H), 3.16 (d, J = 13.2 Hz, 1 H), 3.61−3.70 (m, 2 H), 3.65 (s, 3 H), 7.04−7.35 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.71 (t, J = 19.3 Hz, 1 C), 37.93, 40.72, 51.68, 55.50, 59.83, 60.15, 60.76, 126.46, 126.92, 128.24 (4 C), 128.66 (2 C), 129.57 (2 C), 138.27, 139.16, 176.34 ppm. $C_{21}H_{24}DNO_2$ (324.43): calcd. C 77.74, H 8.08, N 4.32; found C 78.05, H 7.80, N 4.27.

Methyl (3*S,4*S**)-1,3-Dibenzyl-4-but-3-enylpyrrolidine-3-carboxylate (14):** Prepared according to procedure B from **3** (491 mg, 2 mmol). After 24 hours at room temperature, a solution of allyl bromide (350 μL, 4 mmol) in degassed THF was added at room temperature and the mixture stirred for 24 hours. After work up, the residue was chromatographed with cyclohexane/EtOAc (80:20) as eluent to give **14** (385 mg, 57%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3029, 2932, 2852, 2793, 2660, 1732, 1449, 1257, 1212, 904, 862, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46−1.56 (m, 1 H), 1.91−2.14 (m, 3 H), 2.35−2.45 (m, 2 H), 2.46 (d, J = 9.6 Hz, 1 H), 2.80 (d, J = 13.2 Hz, 1 H), 2.89−2.96 (m, 1 H), 3.03 (d, J = 9.6 Hz, 1 H), 3.19 (d, J = 13.2 Hz, 1 H), 3.58−3.68 (m, 2 H), 3.65 (s, 3 H), 4.96−4.99 (m, 1 H), 5.01−5.05 (m, 1 H), 5.82 (ddt, J = 17.0, 10.0, 6.4 Hz, 1 H), 7.04−7.35 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.75, 32.79, 37.79, 45.92, 51.70, 55.62, 58.98, 59.87, 60.17, 114.93, 126.48, 126.95, 128.22 (2C), 128.28 (2C), 128.64 (2C), 129.67 (2C), 138.25, 138.37, 139.20, 176.18 ppm. $C_{24}H_{29}NO_2$ (363.22); calcd. C 79.30, H 8.04, N 3.85; found C 78.33, H 7.92, N 3.90.

Methyl (3*S,4*S**)-1,3-Dibenzyl-4-iodomethylpyrrolidine-3-carboxylate (15):** Prepared according to procedure B from **3** (491 mg, 2 mmol). After 24 hours at room temperature, a solution of iodine (1 g, 4 mmol) in degassed THF (5 mL) was added at 0 °C. The cold bath was removed and the reaction mixture stirred at room temperature until completion. The reaction was hydrolysed with an aqueous solution of NH_4Cl/NH_4OH (2:1). The layers were separated, the aqueous one being extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents evaporated under reduced pressure. The residue was chromatographed with cyclohexane/EtOAc (80:20) as eluent to give **15** (512 mg, 58%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3084, 3061, 3027, 2948, 2792, 1731, 1603, 1494, 1454, 1434, 1272,

1216, 744, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.63−3.70 (m, 1 H), 2.67 (d, *J* = 9.7 Hz, 1 H), 2.87 (d, *J* = 12.9 Hz, 1 H), 2.90−2.96 (m, 1 H), 2.99 (d, *J* = 9.7 Hz, 1 H), 3.05−3.10 (m, 1 H), 3.09 (d, *J* = 12.9 Hz, 1 H), 3.25 (dd, *J* = 12.2, 9.2 Hz, 1 H), 3.64 (s, 2 H), 3.65 (s, 3 H), 3.72 (dd, *J* = 9.2, 3.6 Hz, 1 H), 6.98−7.01 (m, 2 H), 7.16−7.34 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.60, 37.00, 48.99, 52.00, 56.60, 59.77 (2C), 60.52, 126.84, 127.11, 128.36 (4C), 128.66 (2C), 129.61 (2C), 137.16, 138.92, 175.03 ppm. This compound is too unstable to give satisfactory elemental analysis.

Acknowledgments

Thanks are due to Monique Baudry for the preparation of starting materials and to the Ministère de la Recherche et de l'Enseignement Supérieur for a grant (to F. D.)

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Received June 28, 2002
[O02356]