RAPID AND EFFICIENT ACCESS TO *MESO*-2,5-*CIS*-DISUBSTITUTED PYRROLIDINES BY DOUBLE AZA-MICHAEL REACTIONS OF CHIRAL PRIMARY AMINES

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Abstract – The double aza-Michael reaction of enantiopure primary amines on bis α,β-unsaturated diesters has been studied under various activating conditions. High pressure allowed a rapid and efficient access to *meso*-2,5-disubstituted pyrrolidines.

INTRODUCTION

2,5-Disubstituted pyrrolidines are naturally ubiquitous, biologically important substances and the synthesis of this type of alkaloids is of considerable current interest.[1] Access to pyrrolidine moiety can be envisaged through an aza-Michael addition on a mono or bis α,β-unsaturated ester: our research group has contributed to the synthesis of 2,5-dialkylpyrrolidines using intramolecular conjugate addition of an enamino ester resulting from the condensation of (*R*)-1-phenylethylamine to ketoenedioate (Scheme 1).[2]

In fact, the aza-Michael addition to unsaturated esters is undoubtedly one of the most direct methods to synthesize β-amino acids and pyrrolidines through both inter- and intra-molecular pathways respectively. In this area, the conjugate addition of enantiomerically pure lithium amides as homochiral ammonia

equivalents is known to be the most efficient route to prepare β-amino acids.[3] However, applied to dialkyl
(*E,E*)-octa-2,6-dienoates, the addition of lithium amide led to the homochiral aminocyclopentane *via* a
tandem conjugate addition-intramolecular cyclisation process.[4]
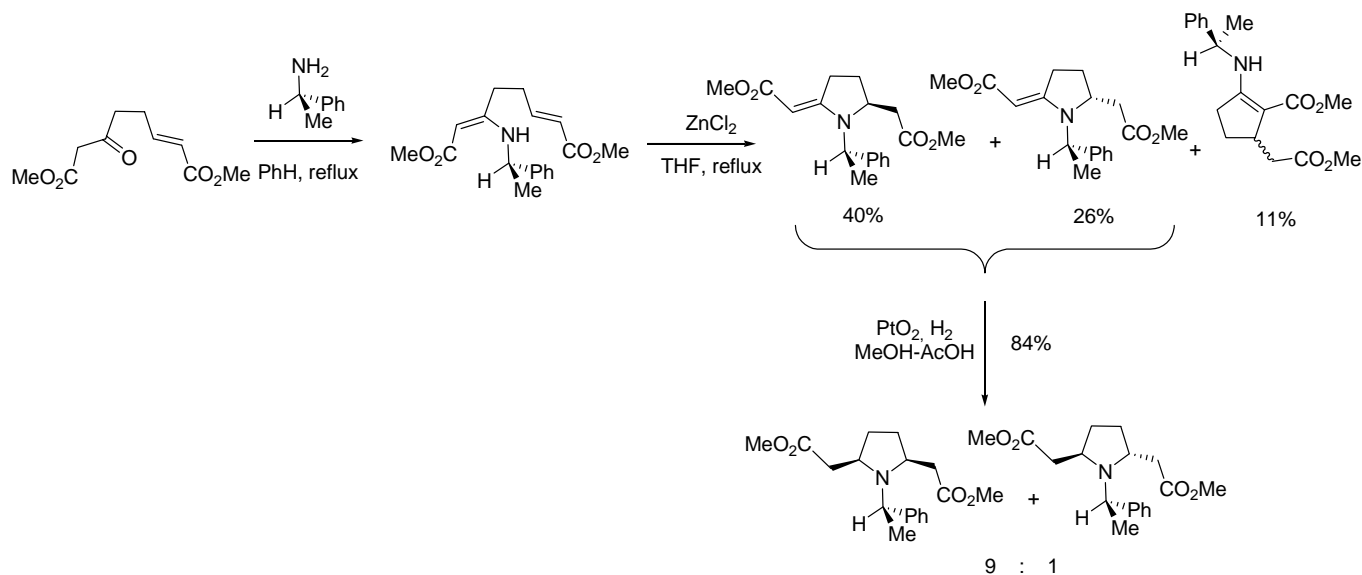
Scheme 1

Furthermore, the 1,4-addition of primary amines is restricted by steric effect of the α/β-substituents
bearing by the unsaturated ester and generally require either high temperature, high pressure, microwave
irradiation or Lewis acid catalysis:[3] Maddaluno has recently described hyperbaric tandem aza-Michael
addition of primary amines to the cyclic bielectrophile derived from cyclohexane-1,4-dione to prepare
azanorbornane skeleton.[5] In turn, Murray has circumvented the problem related to steric disfavored
effects using hydroxylamine, small and very reactive primary amine, and has efficiently synthesized
2,5-disubstituted *N*-hydroxypyrrolidines by consecutive double 1,4-addition to diethyl
octa-2,6-dienedioate at room temperature.[6]

In this paper, we report an efficient and general method to prepare orthogonally functionalized
meso-2,5-disubstituted pyrrolidines by double conjugate addition reactions of enantiopure primary amines
to dimethyl, di*tert*-butyl or dibenzyl octa-2,6-dienedioates. We have demonstrated that the double
1,4-addition of primary amines requires activation and various activating conditions such as high pressure,
microwave irradiation or catalysis have been studied.

RESULTS AND DISCUSSION

The symmetrical dialkyl octa-2,6-dienedioates (**4a-c**) were synthesized, on multigram scale, in two steps
starting from 1,5-cyclooctadiene (**2**) using an ozonolysis and a subsequent Wittig reaction (Scheme 2).
The Wittig reagents (**1a-c**), (methoxy-, *tert*-butoxy- and benzyloxy-carbonylmethylene)triphenyl-

phosphoranes, were prepared according to a procedure adapted from the literature with excellent yields over two steps starting from alkyl bromoacetates.[7]

Then, ozonolysis of 1,5-cyclooctadiene (**2**) followed by the treatment with an excess of triphenylphosphine gave, after distillation of the crude mixture, the unstable succinic aldehyde (**3**) in 98% yield (Scheme 2).[8] This dialdehyde was directly converted by a double Wittig reaction using a slight excess of (alkoxycarbonylmethylene)triphenylphosphorane into the corresponding symmetrical bis α,β-unsaturated diester (**4a-c**) (Scheme 2).[9] These dienoates were efficiently synthesized as a mixture of *Z/Z*, *E/Z*- and *E/E*-isomers separable by column chromatography. The *Z/Z*: *E/E* ratio was mostly in favor of the *E/E* isomer, depending on the steric hindrance of the alkoxy substituents: the dimethyl ester **4a** was obtained in a 1: 9 *Z/Z*: *E/E* ratio and the dibenzyl ester **4c** in a 2: 98 *E/Z*: *E/E* ratio. In the case of the bulky *tert*-butyloxy group, the diester **4b** was isolated as the single *E/E* isomer.
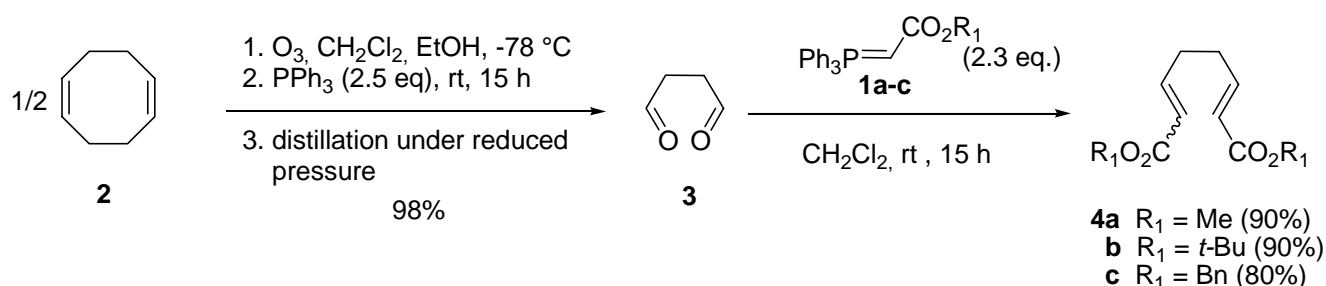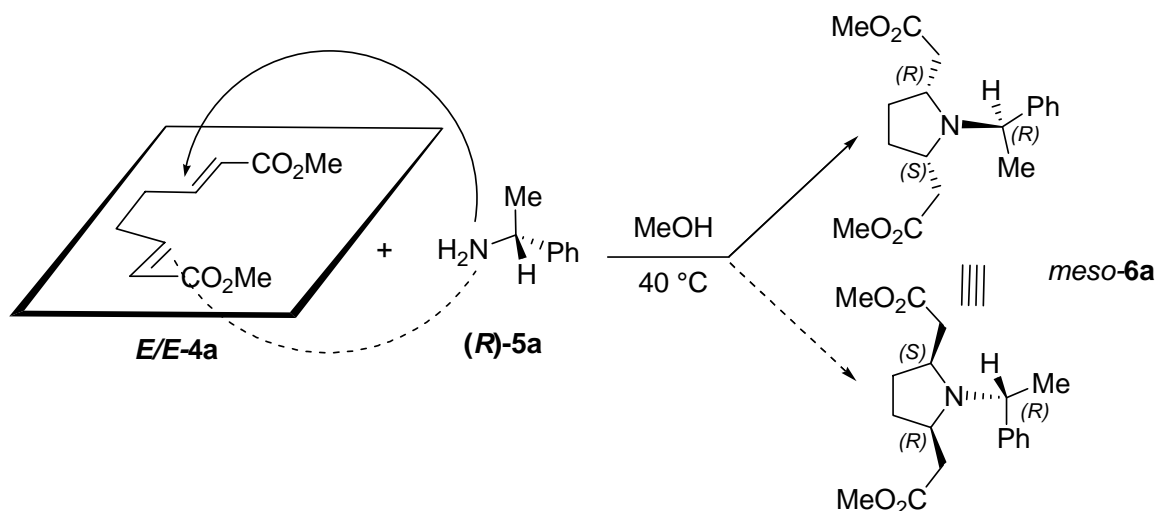

Scheme 2

Then, we have studied the bis conjugate addition of both commercially available (*S*)- and (*R*)-α-methylbenzylamine **5a**, and (*R*)-phenylglycinol[10] **5b**.
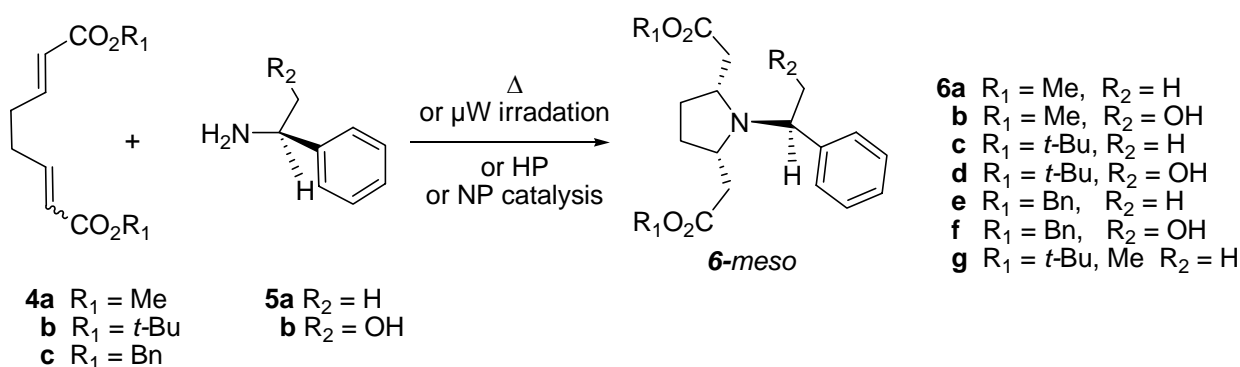
Scheme 3

We first examined the addition of chiral α-methylbenzylamine **5a** to dimethyl *E,E*-octa-2,6-dienedioate **4a** (Scheme 3 and Table 1). To optimize the reaction conditions, solvent effect was explored using a molar solution of diene in various solvents. The reaction is monitored by ^{1}H NMR until the dienedioate is entirely consumed.

Previous reports have showed that addition of amine to α,β-unsaturated esters was most efficient in protic solvents.[11] We confirmed that the reaction did not proceed using non protic solvents such as toluene, THF or acetonitrile in the presence of DBU[12] as a base (Table 1, entries 1-4). Moreover, the reaction proceeded smoothly under solvent-free conditions. Using methanol as solvent allowed the access to the bis-adduct **6a** but highly prolonged reaction time, 2 weeks, was required (Table 1, entries 5-9). In refluxing methanol, the yield dramatically decreased due to the diene degradation. The best yields were obtained when the reaction was performed at 40 °C (Table 1, entries 7-10). As a result, we have adopted methanol and 40 °C respectively as the optimal solvent and reaction temperature for the following investigation. On the opposite of the addition of hydroxylamine,[6] the 1,4-addition of (*R*)-α-methylbenzylamine (***R***)-**5a** to dimethyl *E,E*-octa-2,6-dienedioate **4a** only gave the thermodynamic pseudo-*meso*-pyrrolidine 2,5-*cis*-disubstituted **6a** which presented the same NMR data and the same specific rotation as those reported in the literature[2] (Scheme 4). We never observed the formation of the *trans* isomer.

Scheme 4

Starting from the Z/Z isomer of **4a**, the conjugate addition of the (*R*)- α-methylbenzylamine afforded the same *cis*-pyrrolidine **6a** in good yield (Table 1, entry 8): the diastereoselectivity of the diene had no influence on both the rate and the stereoselectivity of the reaction. For the following exploration, the dimethyl octa-2,6-dienedioates will, then, be used as a mixture of *E/E* and *Z/Z* isomers in a 9:1 ratio.

As the addition reaction needed a prolonged time under atmospheric pressure to afford the pyrrolidine adduct in reasonable yields, we have then investigated the effect of activation agents such as high pressure, microwave irradiation and catalysis using natural phosphates (NP). In this area, Zahouily has recently developed a novel catalyzed aza-Michael reaction in mild conditions: the use of natural phosphate (NP) and potassium fluoride doped natural phosphate (KF/NP) as catalysts in methanol accelerates at room temperature the addition reaction of aromatic amines or benzylamine on chalcones and alkyl acrylates.[13] Unfortunately, in the case of the dimethyl octa-2,6-dienedioate **4a** no enhancement of the rate of the double conjugate addition was observed (Table 1, entries 11-13). These results could be first explained by the low reactivity of the diester **4a** compared to Michael acceptors employed in the published study and by the disfavored steric hindrance of the α-methylbenzylamine compared to benzylamine.

Otherwise, microwave irradiation is known to activate the rate of organic reaction and efficiently promotes Michael additions allowing shorter reaction times.[14] The effects of the microwave irradiation are not clearly established: it is assumed that the rate enhancement is partially due to dipole-dipole interactions between the electromagnetic field and polar compounds whose orientation alternates at a very high frequency leading to dielectric heating. Under microwave irradiation (250 W, 150 °C), the conjugate addition of (*S*)-α-methylbenzylamine to the dienediester **4a**, was activated and led to the *cis*-pyrrolidine **6a** in only 10.5 hours in moderate yield due to the diene degradation at high temperature (Table 1, entry 14).

Finally, an alternative to circumvent the limitations of the high temperature sensitive diene and the disfavored steric hindrance consists in resorting to high pressure. It is well established that the rate of the Michael addition could be accelerated by high pressure activation without modifying its regio- and stereoselectivity and allowing improved yield and cleaner reaction. Moreover, high pressure has already successfully been employed to activate the 1,4-addition of bulky amines to chiral crotonates affording β-amino esters.[15] The acceleration of the reaction under hyperbaric conditions is correlated to the activation volume associated which has to be large and negative (typically from -10 to -70 mL/mol). Jenner has measured a highly negative activation volume associated to the aza-Michael addition explaining the efficiency of the high pressure activation.[16] Thus, applied to the dimethyl dienedioate **4a**, the hyperbaric addition (11 kbar) of the amine (***S***)-**5a** gave the pyrrolidine **6a** at room temperature after 42 h in excellent yield (Table 1, entry 15).

Table 1 Double aza-Michael reaction of α-methylbenzylamine to dimethyl octa-2,6-dienedioate **4a**

Entries	Eq of amine 5a	Z/Z :E/E ratio (4a)	Solvent	Reaction conditions	Product 6a Yield (%)[a]
1	(R)1.5 eq	0 : 1	THF	rt, 15 days	start. mat.[e]
2	(R)1.5 eq	0 : 1	THF	reflux, 15 days	decomposition
3	(R)1.5 eq	0 : 1	toluene	rt, 15 days	start. mat.[e]
4	(R)1.5 eq	0 : 1	MeCN	rt, DBU (0.5 eq),[11] 15 days	start. mat.[e]
5	(R)1.5 eq	0 : 1	MeOH	rt, 15 days	80
6	(R)1.5 eq	0 : 1	MeOH	reflux, 15 days	53
7	(R)1.5 eq	0 : 1	MeOH	40 °C, 7 days	92
8	(R)1.5 eq	1 : 0	MeOH	40 °C, 7 days	83
9	(R)1.5 eq	1 : 9	MeOH	40 °C, 7 days	93
10	(S) 1.5 eq	1 : 9	MeOH	40 ºC, 5 days	70
11	(S) 1.5 eq	1 : 9	MeOH	40 ºC, 5 days, NP[b,13]	70
12	(S) 1.5 eq	1 : 9	MeOH	40 ºC, 5 days, Na/NP[c]	66
13	(S) 1.5 eq	1 : 9	MeOH	40 ºC, 5 days, KF/NP[d, 13]	75
14	(S) 1.5 eq	1 : 9	MeOH (6 eq), THF	μW, 250W, 150 °C 10.5 h	62
15	(S) 1.5 eq	1 : 9	MeOH (6 eq), THF	11 kbar, rt, 42 h	90

[a] Isolated yield;

[b] NP: natural phosphate;

[c] Na/NP: natural phosphate doped by $NaNO_3$;

[d] KF/NP: natural phosphate doped by KF;

[e] start. mat.: starting materials

After these results, the aza-Michael addition was extended to the (R)-phenylglycinol **5b** (Scheme 3 - Table 2): the heterocycle **6b** was isolated in poor yield using prolonged thermal and NP catalyzed activations but the starting diene was recovered (Table 2, entries 1-4). The activation by the piezoprocess was also fruitless: a small amount of pyrrolidine **6b** was only isolated and we observed that the decomposition of the diene began after 4 h of reaction (Table 2, entry 5). An explanation of the low conversion rate could be that the amino alcohol **5b** is more sterically hindered than its homologue **5a**. Again, the hyperbaric process was the appropriate method to skirt round this constraint: after 42 h at 11 kbar and room temperature, the pyrrolidine **6b** was obtained in excellent yield (Table 2, entry 6).

Table 2 Double aza-Michael reaction of (*R*)-phenylglycinol **5b** to dimethyl octa-2,6-dienedioate **4a**

Entries	Eq of amine 5b	Z/Z :E/E ratio (4a)	Solvent	Reaction conditions	Product 6b Yield (%)[a]
1	1.5 eq	1 : 9	MeOH	40 ºC,18 days	35
2	1.5 eq	1 : 9	MeOH	40 ºC, 18 days, NP[b]	35
3	1.5 eq	1 : 9	MeOH	40 ºC,18 days, Na/NP[c]	30
4	2 eq	1 : 9	MeOH	40 ºC,18 days, KF/NP[d]	33
5	1.2 eq	1 : 9	MeOH (6 eq), THF	µW, 250W, 150 °C, 10 h	15 decomposition
6	1.2 eq	1 : 9	MeOH (6 eq), THF	11 kbar, rt, 42 h	90

[a] Isolated yield;

[b] NP: natural phosphate;

[c] Na/NP: natural phosphate doped by $NaNO_3$;

[d] KF/NP: natural phosphate doped by KF.

The following studies have successively concerned the di*tert*-butyl and the dibenzyl octa-2,6-dienedioates **4b** and **4c** and the results have been stored in the Tables 3 and 4 (Schemes 7 and 8).

When the conjugate addition took place in methanol, the prolonged reaction time until the total consumption of the di-*tert*-butyl or dibenzyl diesters conduced to a mixture of mono- and di-transesterified pyrrolidines accompanying the desired pyrrolidines **6c** and **6e** respectively. Using the secondary alcohol *iso*propanol (*i*PrOH) and the tertiary alcohol *tert*-butanol (*t*BuOH) avoided the competitive reaction. In general, the encumbrance of the ester function led to a drop in conversion rate and an increase of the reaction time. Under thermal activation, when the conjugate addition of the di*tert*-butyl *E,E*-octa-2,6-dienedioates **4b** to the amine **5a** was carried out in methanol, the paralleled transesterification occurred giving a mixture of the 2,5-*cis* disubstituted pyrrolidines **6a**, **6c** and of the two diastereomers of **6g** (Table 3, entry 1). Unfortunately, in *i*PrOH, the addition did not take place at 40 °C after 15 days and the starting bis Michael acceptor was entirely recovered (Table 3, entry 2).

Catalysis by NP and doped NP was also inefficient and the dienoate **4b** remained unchanged (Table 3, entries 3-5). Moreover, whatever the power used for the microwave irradiation activation, only the degradation of the starting *tert*-butyl diester was observed and the pyrrolidine **6c** has never been isolated (Table 3, entry 6).[15]

Only the hyperbaric addition allowed the access to the pyrrolidines. In the presence of methanol as external proton donating agent, the diene was converted at 11 kbar and room temperature in an inseparable mixture of the major desired heterocycle **6c** and the minor transesterified analogue **6a** in good

yield (Table 3, entry 7). Replacing methanol by *iso*propanol or by *tert*-butanol led the expected bis adduct **6c** with excellent yield avoiding the competitive reaction (Table 3, entries 8 and 9).

Finally, all attempts of 1,4-addition of the phenylglycinol **5b** to the di-*tert*butyl dienedioate **4b** failed under thermal or NP catalyzed activation. Similarly, the conjugate addition activated by high pressure gave the pyrrolidines **6d** in reasonable yield after 4 days at 11 kbar and at 35 ° C (Table 3, entry 10).

Table 3 Double aza-Michael reaction of chiral primary amines to di-*tert*-butyl dienediester **4b**

Entries	R_2	Eq of amine	Solvent	Reaction conditions	Results Yield (%)[a]
1	H	(*S*)1.2 eq	MeOH	40 °C, 15 days	**6a** 19 **6g** 10 **6c** 28
2	H	(*S*)1.2 eq	*i*PrOH	40 °C, 15 days	start. mat.[e]
3	H	(*S*) 2 eq	*i*PrOH, H_2O (6 eq)	40 °C,15 days, NP[b]	start. mat.[e]
4	H	(*S*) 2 eq	*i*PrOH, H_2O (6 eq)	40 °C, 15 days, Na/NP[c]	start. mat.[e]
5	H	(*S*) 2 eq	*i*PrOH, H_2O (6 eq)	40 °C, 15 days, KF/NP[d]	start. mat.[e]
6	H	(*S*) 2 eq	THF, *i*PrOH (6 eq)	μW, 100 W, 50 °C or 100 °C, 3.5 h	degradation
7	H	(*S*)1.2 eq	THF, MeOH (6 eq)	11 kbar, rt, 42 h	**6a** 7 **6c** 64
8	H	(*S*)1.2 eq	THF, *t*BuOH (6 eq)	11 kbar, 35 °C, 15 h	**6c** 80
9	H	(*S*)1.2 eq	THF, *i*PrOH (6 eq)	11 kbar, 35 °C, 15 h	**6c** 90
10	OH	(*R*)1.2 eq	THF, *i*PrOH (6 eq)	11 kbar, 35 °C, 4 days	**6d** 60

[a] Isolated yield;

[b] NP: natural phosphate;

[c] Na/NP: natural phosphate doped by $NaNO_3$;

[d] KF/NP: natural phosphate doped by KF;

[e] start. mat.: starting materials.

In the case of the dibenzyl *E,E*-octa-2,6-dienedioates **4c**, the same observations were made: (i) in the presence of methanol, transesterification occurred (Table 4, entries 2 and 4); (ii) NP or doped catalysis did not have significant influence on the conversion rate (Table 4, entries 5-7); (iii) using microwave activation (250 W), the starting diene **4c** decomposed at high temperature (150 °C or 200 °C) (Table 4, entry 8); (iv) at 11 kbar and 35 °C, in the presence of *tert*butanol, the pyrrolidines **6e** was isolated in acceptable yield after 5 days (Table 4, entry 10).

In the same hyperbaric reaction conditions, the conjugate addition of the amino alcohol **5b** to the dibenzyl

dienoate **4c** led to the *cis*-pyrrolidine **6f** in poor yield (Table 4, entry 11).

Table 4 Double aza-Michael reaction of chiral primary amines to dibenzyl octa-2,6-dienedioate **4c**

Entries	R_2	Eq of amine	Solvent	Reaction conditions	Results Yield (%)[a]
1	H	(*S*) 1.5 eq	*i*PrOH	40 °C, 18 days	**6e** 15
2	H	(*S*) 1.5 eq	*i*PrOH, MeOH (6 eq)	40 °C, 20 days, Na/NP[c]	**6e** 74 **6c** 6
3	H	(*S*) 1.5 eq	*i*PrOH, H$_2$O (6 eq)	40 °C, 9 days	**6e** 58
4	H	(*S*) 1.5 eq	MeOH	40 °C, 5 days, Na/NP[c]	**6e** 45 **6c** 11
5	H	(*S*) 1.5 eq	*i*PrOH, H$_2$O (6 eq)	40 °C, 5-7 days, NP[b]	**6e** 47
6	H	(*S*) 1.5 eq	*i*PrOH, H$_2$O (6 eq)	40 °C, 5-7 days, Na/NP[c]	**6e** 53
7	H	(*S*) 1.5 eq	*i*PrOH, H$_2$O (6 eq)	40 °C, 5-7 days, KF/NP[d]	**6e** 51
8	H	(*S*) 1.5 eq	THF, *i*PrOH (6 eq)	µW, 250 W, 150 °C or 200 °C, 5 h	decomposition
9	H	(*S*) 1.5 eq	THF, *i*PrOH (6 eq)	11 kbar, 35 °C, 5 days	**6e** 30
10	H	(*S*) 1.5 eq	THF, *t*BuOH (6 eq)	11 kbar, 35 °C, 5 days	**6e** 60
11	OH	(*R*) 1.5 eq	THF, *t*BuOH (6 eq)	11 kbar, 35 °C, 5 days	**6f** 24

[a] Isolated yield;

[b] NP: natural phosphate;

[c] Na/NP: natural phosphate doped by NaNO$_3$;

[d] KF/NP: natural phosphate doped by KF.

Carbon-carbon and carbon-hydrogen connectivities in all pyrrolidines were unambiguously determined by two-dimensional NMR spectroscopy and the absolute structure confirmation was made by nOesy experiments (Figure 1). In these series of pyrrolidines, only one conformer is observed due to the absence of rotameric equilibria. Indeed, a symmetric ^{1}H-NMR spectrum usually indicates the *cis*-stereochemistry.[22] Nevertheless, in our case, the ^{1}H- and ^{13}C-NMR spectra are completely desymmetrized even at high temperature (performed in *d*[6]-DMSO) revealing the lack of free rotation of the substituting nitrogen group around the N-C* bound (Figures 2 and 3). Noteworthy, the chemically equivalent ^{1}H and ^{13}C in the cyclic compound are magnetically different owing to the fact that, in the unique rotamer, the phenyl anisotropy effect is only affected a part of the molecule.
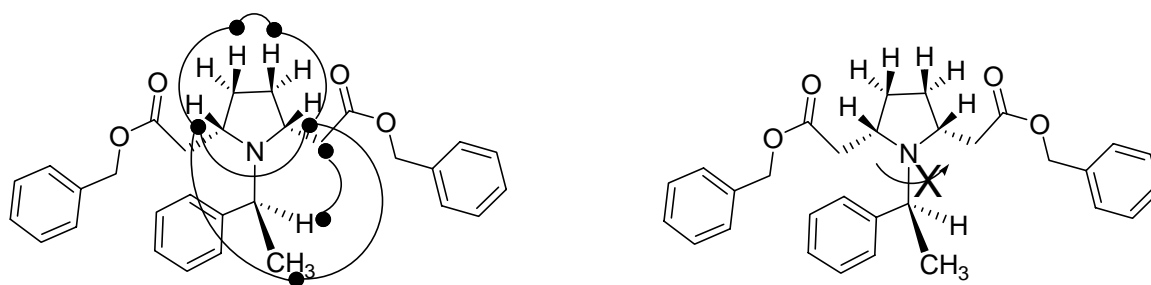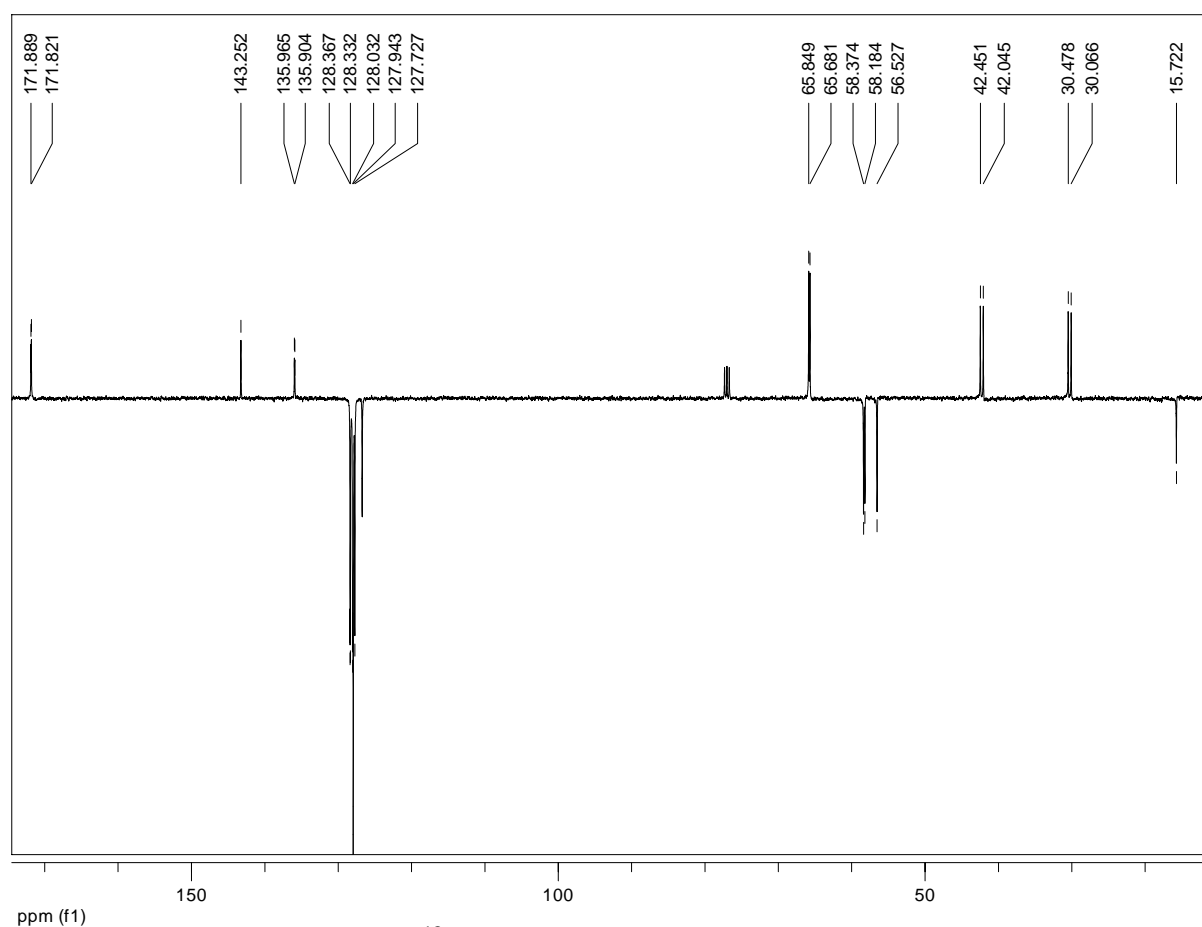
Figure 1: nOesy data for pyrrolidine 6e

Figure 2: ^{13}C-NMR spectrum for pyrrolidine 6e

CONCLUSIONS

The chemistry described above provides a convenient and efficient method to prepare a series of orthogonally functionalized *meso*-2,5-disubstituted pyrrolidines by double conjugate addition reactions of enantiopure primary amines to alkyl octa-2,6-dienedioates. Our method gave access to pyrrolidines in two steps starting the succinaldehyde. The key step is based on a double aza-Michael addition of a primary amine to a dialkyl octa-2,6-dienedioate which is more efficient under hyperbaric conditions. The

application of these results to the synthesis of compounds of biological relevance and of C_2-symmetric pyrrolidines is in progress.
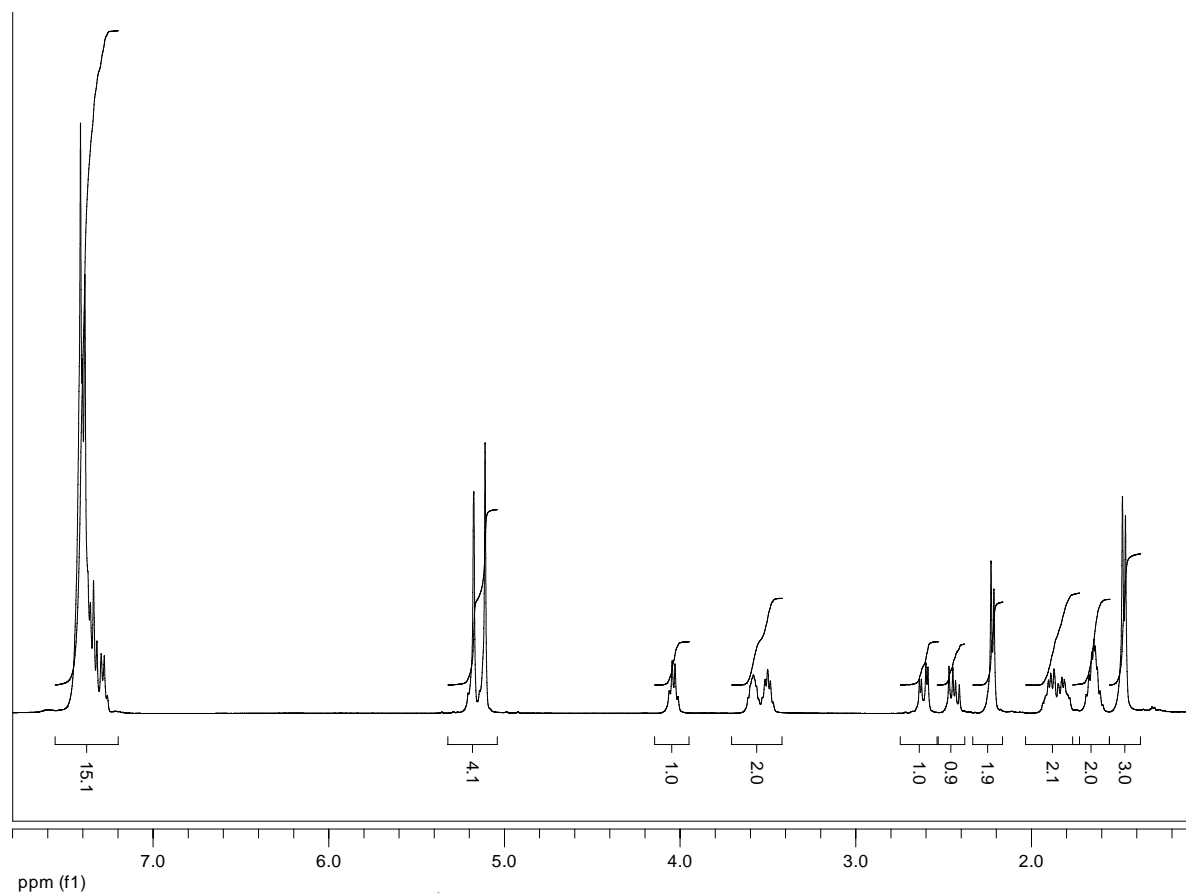
Figure 3: ^{1}H-NMR spectra for pyrrolidine 6e

EXPERIMENTAL

General

Commercial reagents were used without purification. Prior to use, THF was freshly distilled from sodium benzophenone, methanol and *iso*propanol from CaH_2. Natural phosphate (NP) came from an ore extracted in the region of Khouribga (it is available in raw form or treated form from CERPHOS Casablanca, Morocco). NP and NP doped with KF (KF/NP) and $NaNO_3$ (Na/NP) have been treated, prepared and generously given by Mohamed Zahouily (Laboratoire de Catalyse, Synthese et Environnement, Faculty of Sciences and Techniques, University Hassan II, Morocco). Treatment consisted in techniques involving attrition, sifting, calcination, washing and recalcination.[18] All anhydrous reactions were carried out under argon atmosphere. Analytical thin layer chromatography was performed on Merck 60F-254 coated silica (0.2 mm) on glass and was revealed by UV-light and Kägi-Misher or Dragendorf reagent. All flash chromatography separations were performed with Merck Kieselgel (40-63 µm). Melting points were recorded on an Electrothermal digital apparatus and were uncorrected. Infrared (IR) spectra were obtained as neat films and were recorded on Bruker Vector 22 spectrophotometer. ^{1}H, ^{31}P and ^{13}C spectra were

recorded respectively at 200, 300 and 400 MHz, 80.96 MHz and 50, 75, 100 MHz unless otherwise specified. CDCl$_3$ was used as internal reference. Specific rotations [α]$_D$ were measured on a PolAAr32 polarimeter with sodium (589 nm) lamp at 20 °C in a 1 dm cell and were given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations were quoted in g per 100 mL. The electron impact (EI) mass spectra were run on a HP 6890 series-GC system spectrometer at 70 eV ionizing voltage and equipped with HP 5973 mass selective detector. Elemental analyses were performed by the Service de Microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin-Elmer 2400 analyser.

(Alkoxycarbonylmethyl)triphenylphosphonium bromide : general procedure[7]

A 1 L erlenmeyer fitted with a dropping funnel and a magnetic stirrer was charged with 65.5 g (0.25 mol, 1 eq.) of triphenylphosphine and 150 mL of toluene. The reaction mixture was cooled by a cold water bath and alkyl bromoacetate (0.25 mol, 1 eq.) was slowly added dropwise. The reaction was allowed stirring at rt overnight and the phosphonium salt was filtered. The salt was washed twice with 150 mL of pentane and dried.

(Methoxycarbonylmethyl)triphenylphosphonium bromide[19] (Colorless solid, Yield = 95%). mp 163 °C.

(*tert*-Butoxycarbonylmethyl)triphenylphosphonium bromide (Colorless solid, Yield = 93%). mp 176 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.18 (9H, s), 5.35 (2H, d, J^2_P = 14.1 Hz), 7.66 (6H, td, J^3 = 7.8, J^4_P = 3.6 Hz), 7.77 (3H, td, J^3 = 7.6, J^4 = 1.4 Hz), 7.88 (6H, ddd, J^3 = 7.1, J^3_P = 2.1, J^4 = 1.4 Hz). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 27.5 (CH$_3$), 34.2 (CH$_2$, d, J^1_P = 54.0 Hz), 84.6 (C), 117.6 (Car, d, J^1_P = 88.0 Hz), 130.2 (CHar, d, J^3_P = 13.1 Hz); 134.5 (CHar, d, J^2_P = 10.0 Hz), 135.0 (CHar, d, J^4_P = 2.2 Hz), 163.1 (C=O). ^{31}P NMR (CDCl$_3$, 80.96 MHz): δ 22.04 . IR (neat): ν (cm^{-1}) 746 (C-P), 1136 (C-O), 1721 (C=O), 2677 (C Har). Anal. Calcd for C$_{24}$H$_{26}$BrO$_2$P: C, 63.03; H, 5.73. Found: C, 63.1; H, 5.81.

(Benzyloxycarbonylmethyl)triphenylphosphonium bromide (Colorless solid, Yield = 96%). mp 160 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.03 (2H, s), 5.70 (2H, d, J^2_P = 13.9 Hz) 7.12 (2H, dd, J^3 = 7.9, J^4 = 1.7 Hz), 7.23-7.30 (3H, m) 7.57-7.63 (6H, m), 7.72-7.87 (9H, m). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 45.0 (CH$_2$, d, J^1_P = 57.0 Hz); 72.0 (CH$_2$), 120.0 (Car, d, J^1_P = 89.2 Hz), 127.3 (CHar), 127.4 (CHar), 128.0 (CHar, d, J^3_P = 13.2 Hz), 128.7 (CH ar), 131.5 (CHar, d, J^2_P = 10.9 Hz), 133.4 (CHar, d, J^4_P = 2.3 Hz), 140.9 (Car), 171.0 (C=O). ^{31}P NMR (CDCl$_3$, 80.96 MHz) δ 21.84. IR (neat): ν (cm^{-1}) 748 (C-P), 1109 (C-O), 1161(C-C),1486 (C=C), 1721 (C=O). Anal. Calcd for C$_{27}$H$_{24}$BrO$_2$P: C, 66.00; H, 4.92. Found: C,

66.12; H, 5.01.

(Alkoxycarbonylmethylene)triphenylphosphane (1) : general procedure[7]

The salt of phosphonium bromide was dissolved in 2 L of water at rt. The aqueous solution was extracted with 250 mL of Et$_2$O, cooled in an ice bath and five drops of 2% ethanolic phenolphthalein solution were added. 2M aqueous sodium hydroxide was added slowly until the pink endpoint was reached. The solid phosphorane was filtered, washed with cold water and dried. The phosphorane was used for the preparation of the corresponding diester **4** without further purification.

(Methoxycarbonylmethylene)triphenylphosphane (1a)[19] (Colorless solid, Yield = 93%) mp 169 °C.

(*tert*-Butoxycarbonylmethylene)triphenylphosphane (1b)[20] (Colorless solid, Yield = 95 %) mp 158 °C.

(Benzyloxycarbonylmethylene)triphenylphosphane (1c)[20] (Colorless solid, Yield = 97%) mp 120 °C.

Succinic aldehyde (3)[8]

A solution of 1,5-cyclooctadiene (8.82 g, 81.5 mmol) in CH$_2$Cl$_2$ (370 mL) and EtOH (37 mL) was ozonolized at -78 °C until the solution turned light blue. Triphenylphosphine (64.06 g, 244.5 mmol,) was added and the reaction mixture was allowed to warm to rt and stirred for 15 h. After evaporation of the solvent, the crude product was distilled under reduced pression (bp: 63.5 °C ± 1 °C at 12 mm Hg) to yield succinic aldehyde (13.10 g, 159.8 mmol, Yield: 98%), as a colorless liquid.[23]

Octa-2,6-dienedioic acid dialkyl esters (4): general procedure[9]

To a solution of appropriate ylide (**1**) (97.5 mmol, 2.5 eq.) in anhydrous CH$_2$Cl$_2$ (250 mL) under argon atmosphere, was slowly added the freshly distilled succinic aldehyde (**3**) (3.20 g, 39 mmol, 1 eq.) and the mixture was stirred at rt overnight. The solvent was removed under vacuum. 100 mL of Et$_2$O was added and the suspension was cooled to 0 °C in an ice-water bath in order to eliminate a large amount of triphenylphosphine oxide. The resulting mixture was filtered and the solid was washed twice with cool Et$_2$O (2 x 50 mL). The solvent was evaporated and the residue was purified by silica gel flash chromatography using as the eluent a mixture of cyclohexane/EtOAc in a 90:10 ratio.

(2*E*,6*E*)-Octa-2,6-dienedioic acid dimethyl ester (4a)[21]

Compound **4a** (6.95 g, 90%) was obtained as a colorless liquid (bp 95°C / 0.15 mmHg).

(2*E*,6*E*)-Octa-2,6-dienedioic acid di-*tert*-butyl ester (4b)[4d]

Similar reaction gave **5b** (9.91 g, 90%) as a colorless solid (mp 67-68°C).

(2*E*,6*E*)-Octa-2,6-dienedioic acid dibenzyl ester (4c)

Compound **4c** (10.93 g, 80%) was obtained as a colorless syrup. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.39-2.41 (4H, m), 5.20 (4H, s), 5.92 (2H, d, *J* = 15.4 Hz), 6.94-7.06 (2H, m), 7.31-7.43 (10H, m). ^{13}C NMR (CDCl$_3$, 300 MHz): δ   30.4 (CH$_2$), 66.2 (CH$_2$), 122.0 (CH), 128.2 (CHar), 128.4 (CHar), 128.6 (CHar), 136.0 (Car), 147.5 (CH), 166.6 (C=O). IR (neat): ν (cm^{-1}) 1148 (C-C), 1263(C-O), 1654 (C=C), 1715 (C=O), 2942 (C-H). Anal. Calcd. for C$_{22}$H$_{22}$O$_4$: C, 75.41; H, 6.33. Found: C, 75.26; H, 6.42.

General procedure for the synthesis of pyrrolidines (6a-f)

The *cis*-pyrrolidines were prepared from the corresponding diester (**4a-c**) by the following general methods. Refer to Tables 1,2,3 and 4 for isolated yield, method type and reaction conditions.

Method A: Activation by microwave irradiation

In a 10 mL microwave glass tube were placed diester compound **4** (1 mmol), enantiopure primary amine **5** (1.5 mmol), alcohol (6 mmol), THF (1 mL) and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Enhanced microwave irradiation (250-300 W) was used, the temperature being ramped from rt to 50-200 °C. Once the temperature was reached, the reaction mixture was held for 5-10.5 h. Then, the mixture was allowed to cool to rt, the reaction vessel was opened and the solvent was evaporated under reduced pressure. The oily residue was purified by flash chromatography on silica gel eluting with using as the eluent a mixture of cyclohexane/EtOAc in a 95:5 to 70:30 ratio to afford the desired pyrrolidine **6**.

Method B: Activation by high-pressure

A solution of diester compound **4** (1 mmol) and enantiopure primary amine **5** (1.2-1.5 mmol) in a mixture alcohol (6 mmol) in THF was introduced by means of a syringe through the capillary inlet of a 1 mL Pyrex glass cell. The cell was placed into the high-pressure apparatus and pressurized under 0.9 GPa at 20 °C for 7 h or 5 days. After depressurization, the solvent was evaporated and the oily residue was purified by silica gel flash chromatography using as the eluent a mixture of cyclohexane/EtOAc in a 95:5 to 70:30 ratio to yield pure pyrrolidine **6**.

Method C: Activation by thermal conditions

To a solution of diester compound **4** (1 mmol) in alcohol (MeOH, *i*PrOH or *t*BuOH) or in 5 mL of a mixture of alcohol (MeOH, *i*PrOH or *t*BuOH) (6 mmol)/THF or 5 mL of a mixture of water (6 mmol)/alcohol (MeOH, *i*PrOH or *t*BuOH) was added enantiopure primary amine **5** (1.2-1.5 mmol). The mixture was stirred at 30, 40, or 80 °C until completion of the reaction, as monitored by ^{1}H NMR. The

solvent was vacuum evaporated and the residue was purified by silica gel flash chromatography using as the eluent a mixture of cyclohexane/EtOAc in a 95:5 to 70:30 leading to the pyrrolidine **6**.

Method D: Activation by Natural Phosphate

To a round bottom flask containing an mixture of diester compound **4** (1 mmol) and enantiopure primary amine **5** (1.2-1.5 mmol) in alcohol (MeOH, *i*PrOH or *t*BuOH) (1 mL) or MeOH (6 mmol) in iPrOH (1 mL) or 90% aqueous iPrOH (1 mL), NP or Na/NP or KF/NP catalyst (0.1 g) was added and the mixture was stirred at 40°C until completion of the reaction, as monitored by ^{1}H NMR. The reaction mixture was filtered and the catalyst washed with the reactional solvent. After concentration of the filltrate under reduced pressure the residue was subjected to chromatographic purification on silica using as the eluent a mixture of cyclohexane/ EtOAc in a 95:5 to 70:30 leading to the pyrrolidine **6**.

[5-Methoxycarbonylmethyl-1-(1'(*R*)'-phenylethyl)pyrrolidin-2-yl]acetic acid methyl ester (6a)[4] $[\alpha]_D$ -18° (c 1.00, CH$_2$Cl$_2$).

[5-Methoxycarbonylmethyl-1-(2'hydroxy-1'(*R*)'-phenylethyl)pyrrolidin-2-yl]acetic acid methyl ester (6b) $[\alpha]_D$ -51° (c 1.00, CH$_3$OH). ^{1}H NMR (C$_6$D$_6$, 400 MHz): δ 1.07 (1H, m), 1.23 (1H, m), 1.33 (1H, m), 1.48 (1H, m), 2.14 (1H, dd, *J* = 8.8, 15.6 Hz), 2.24 (1H, dd, *J* = 8.7, 15.5 Hz), 2.39 (1H, dd, *J* = 5.2, 10.0 Hz), 2.41 (1H, dd, *J* = 4.6, 11.0 Hz), 3.13 (1H, s), 3.36 (3H, s), 3.40 (3H, s), 3.42 (1H, dd, *J* = 8.6, 4.5 Hz), 3.57 (1H, m), 3.67 (1H, dd, *J* = 4.5, 11.0 Hz), 3.83 (1H, dd, *J* = 4.5, 11.0 Hz), 3.95 (1H, t, *J* = 11 Hz), 7.24 (5H, m). ^{13}C NMR (C$_6$D$_6$, 100 MHz): δ 28.4 (CH$_2$), 29.4 (CH$_2$), 39.3 (CH$_2$), 41.3 (CH$_2$), 49.5 (CH$_3$), 53.8 (CH), 59.2 (CH), 61.0 (CH$_2$), 64.7 (CH), 136.8 (Car), 128.5 (CHar), 128.8 (CHar), 128.0 (CHar), 172.5 (C=O). IR (neat): ν (cm^{-1}) 3449 (OH), 1729 (C=O), 1253 (C-O), 1170 (C-C), 1080 (C-N). GC-MS (EI) *m/z* (%): 304 (100), 262 (12), 244 (8), 230 (11), 91 (9).

[5-*tert*-Butyloxycarbonylmethyl-1-(1'(*R*)'-phenylethyl)pyrrolidin-2-yl]acetic acid *tert*-butyl ester (6c) $[\alpha]_D$ -21° (c 1.00, CCl$_4$). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.40 (9H, s), 1.42 (3H, d, *J* = 6.8 Hz), 1.43 (9H, s) 1.54-1.59 (2H, m), 1.67-1.84 (2H, m), 1.95-2.05 (2H, dd, *J* = 8.5, 15.0 Hz), 2.20 (1H, dd, *J* = 8.7, 15.0 Hz), 2.42 (1H, dd, *J* = 4.8, 15.0 Hz), 3.30-3.37 (1H, m), 3.39-3.46 (1H, m), 3.98 (1H, q, *J* = 6.8 Hz), 7.21 (1H, t), 7.29 (2H, t), 7.36 (2H, d). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 15.9 (CH$_3$), 28.1 (CH$_3$), 30.0 (CH$_2$), 30.4 (CH$_2$), 43.6 (CH$_2$), 44.1 (CH$_2$), 56.9 (CH), 58.0 (CH), 58.4 (CH), 79.9 (C), 80.0 (C), 126.7 (CHar), 127.9 (CHar), 128.0 (CHar), 143.6 (Car), 171.9 (C=O). IR (neat): ν (cm^{-1}) 2974 (C-H), 1723 (C=O), 1148 (C-C), 1083 (C-N). Anal. Calcd for C$_{24}$H$_{37}$NO$_4$: C, 71.46; H, 9.18; N, 3.47. Found: C, 69.16; H, 9.07; N, 3.36.

[5-*tert*-Butyloxycarbonylmethyl-1-(2'hydroxy-1'(*R*)'-phenylethyl)pyrrolidin-2-yl]acetic acid *tert*-butyl ester (6d) $[\alpha]_D$ -60° (c 2.14, CCl$_4$). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.21 (1H, m), 1.37 (1H, m), 1.40 (1H, m), 1. 42 (9H, s), 1.46 (9H, s), 1.71 (1H, m), 2.14 (1H, dd, *J* = 8.8, 15.6 Hz), 2.27 (1H, dd, *J* = 8.7, 15.5 Hz), 2.36 (1H, dd, *J* = 5.2, 10.0 Hz), 2.50 (1H, dd, *J* = 4.6, 11.0 Hz), 3.29 (1H, br), 3.42 (1H, dd, *J* = 4.5, 8.6 Hz), 3. 44 (1H, m), 3.62 (1H, dd, *J* = 4.5, 11.0 Hz), 3.88 (1H, dd, *J* = 4.5, 11.0 Hz), 3.89 (1H, dd, *J* = 10.0, 12.0 Hz), 7.14-7.35 (5H, m). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 28.2 (CH$_3$), 29.8 (CH$_2$), 30.3 (CH$_2$), 42.1 (CH$_2$), 44.5 (CH$_2$), 54.5 (CH), 60,4 (CH), 62.0 (CH$_2$), 65.1 (CH), 80.5 (C), 80.7 (C), 127.9 (CHar), 128.4 (CHar), 128.8 (CHar), 136.8 (Car), 171.4 (C=O), 171.5 (C=O). IR (neat): ν (cm^{-1}) 3438 (OH), 2976 (C-H), 1721 (C=O), 1254 (C-O), 1149 (C-C), 1080 (C-N). GC-MS (EI) *m/z* (%): 388 (43.6), 304 (26.7), 276 (100.0), 230 (13.9), 91 (9.1).

[5-Benzyloxycarbonylmethyl-1-(1'-(*S*)-phenylethyl)pyrrolidin-2-yl]acetic acid benzyl ester (6e)
$[\alpha]_D$ +23° (c 1.00, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.39 (3H, d, *J* = 6.8 Hz), 1.50-1.62 (2H, m), 1.69-1.87 (2H, m), 2.14 (2H, d, *J* = 6.8 Hz), 2.36 (1H, dd, *J* = 14.9, 8.7 Hz), 2.54 (1H, dd, *J* = 14.9, 4.7 Hz), 3.38-3.54 (2H, m), 3.96 (1H, q, *J* = 6.8 Hz), 5.03 (2H, s), 5.09 (2H, s), 7.17-7.37 (m, 15H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 15.67 (CH$_3$), 30.04 (CH$_2$), 30.46 (CH$_2$), 42.02 (CH$_2$), 42.43 (CH$_2$), 56.48 (CH), 58.13 (CH), 58.34 (CH), 65.70 (CH$_2$), 65.86 (CH$_2$), 126.72 (CHar), 127.94 (CHar), 127.95 (CHar), 127.96 (CHar), 128.01 (CHar), 128.05 (CHar), 128.34 (CHar), 128.38 (CHar), 135.88 (Car) ,136.94 (Car), 143.24 (Car), 171.86 (C=O), 171.93 (C=O). IR (neat): ν (cm^{-1}) 2967 (C-H), 1728 (C=O), 1164 (C-C), 1082 (C-N). Anal. Calcd for C$_{30}$H$_{33}$NO$_4$: C, 76.41; H, 7.05; N, 2.97. Found: C, 76.18; H, 6.37; N, 2.92.

[5-Benzyloxycarbonylmethyl-1-(2'-hydroxy-1'(*R*)-phenylethyl)pyrrolidin-2-yl]acetic acid benzyl ester (6f) $[\alpha]_D$ -55° (c 1.00, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.38-1.52 (2H, m), 1.54-1.72 (2H, m), 2.29 (1H, dd, *J* = 14.5, 8.5 Hz), 2.45-2.52 (2H, m), 2.67 (1H, dd, *J* = 14.5, 4.9 Hz), 3.18 (1H, br), 3.50-3.61 (2H, m), 3.64-3.71 (1H, m), 3.87-3.96 (2H, m), 5.11 (2H, s), 5.15 (2H, s), 7.19-7.41 (15H, m). ^{13}C NMR (CDCl$_3$, 300 MHz): δ 29.8 (CH$_2$), 30.5 (CH$_2$), 40.8 (CH$_2$), 42.9 (CH$_2$), 54.6 (CH), 60.4 (CH), 62.1 (CH$_2$), 65.5 (CH), 66.3 (CH$_2$), 66.4 (CH$_2$), 127.9 (CHar), 128.3 (CHar), 128.3 (CHar), 128.3 (CHar), 128.5 (CHar), 128.5 (CHar), 128.6 (CHar), 128.6 (CHar), 128.7 (CHar), 135.8 (Car), 135.8 (Car), 136.7 (Car), 171.8 (C=O). IR (neat): ν (cm^{-1}) 3448 (OH), 2955 (C-H), 1726 (C=O), 1270 (C-O), 1165 (C-C), 1080 (C-N). GC-MS (EI) *m/z* (%): 379 (9), 320 (36), 230 (100), 91 (62).

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