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Stereoselective Tandem Michael-Intramolecular Cyclization Approach to Functionalized Pyrroloisoindolones†

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Abstract: A stereoselective synthesis of pyrrolo[2,1-*a*]isoindol-5-ones is described. The synthesis takes place through a tandem Michael addition-intramolecular cyclization, by the base-promoted condensation of methyl *N*-phthaloylalaninate with conjugate acceptors at low temperature. The desired products were obtained in good yields as single isomers in only one step. Presumably, the stereoselectivity of the cyclization step is kinetically controlled by a lithium chelate species between the interacting centers. The structure of the adducts is discussed, being supported by NMR experiments and X-ray crystallography. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Pyrroloisoindolones; *N*-phthaloylalaninate; Michael reactions; cyclization

INTRODUCTION

The intramolecular cyclization of *N*-substituted phthalimides has been a subject of considerable attention in the last decades. This has been mainly due to the mechanistic aspects of the process itself, and to the synthetic potential of the resultant products. Photoinduced electron transfer cyclization reactions[1] of *N*-phthaloylamino acids,[2] silylphthalimides,[3] dicarboximide Mannich bases,[4] *N*-thioalkylphthalimides,[5] and *N*-(2-alkenyl)phthalimides[6] have been intensively studied. Carbanionic cyclizations have been also developed, via

† Dedicated to the memory of Professor A. Héber Muñoz pioneer in this research.

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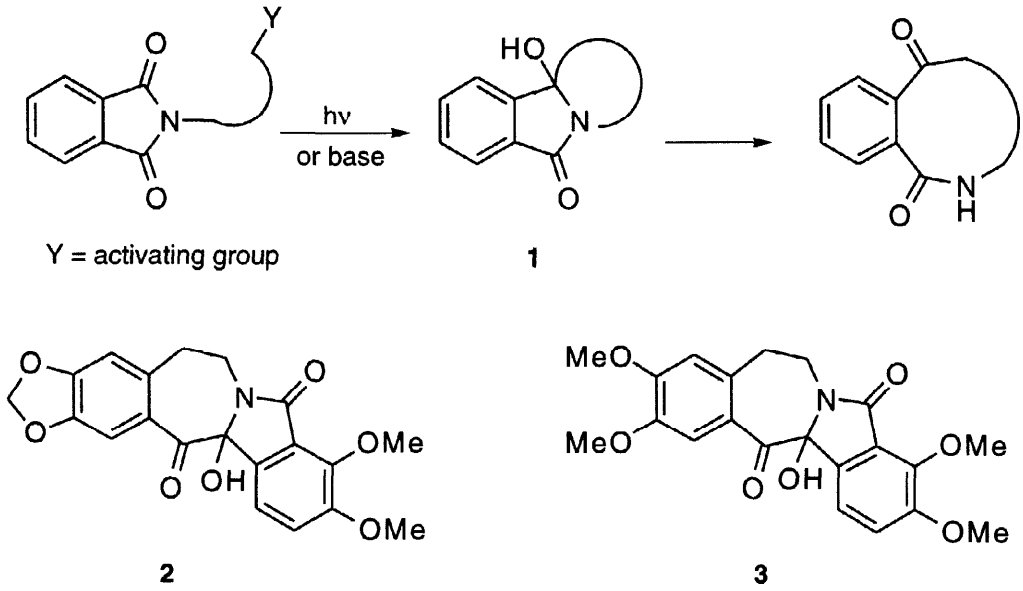
N-phthalimido-substituted phosphoranes,[7] phosphonates,[8] β-keto esters,[9] and α-bromo esters.[10] These methods have proven to be efficient synthetic routes to medium size heterocycles and macrocycles.[3c,11] Hydroxy cyclo[2,1-*a*]isoindolones, **1**, have been obtained as major products or as intermediates in the formation of macrocycles by expansion of the hydroxyisoindolone moiety (Scheme 1). Chilenine (**2**), and palmanine (**3**) are some examples of natural alkaloids possessing this skeleton.[12]



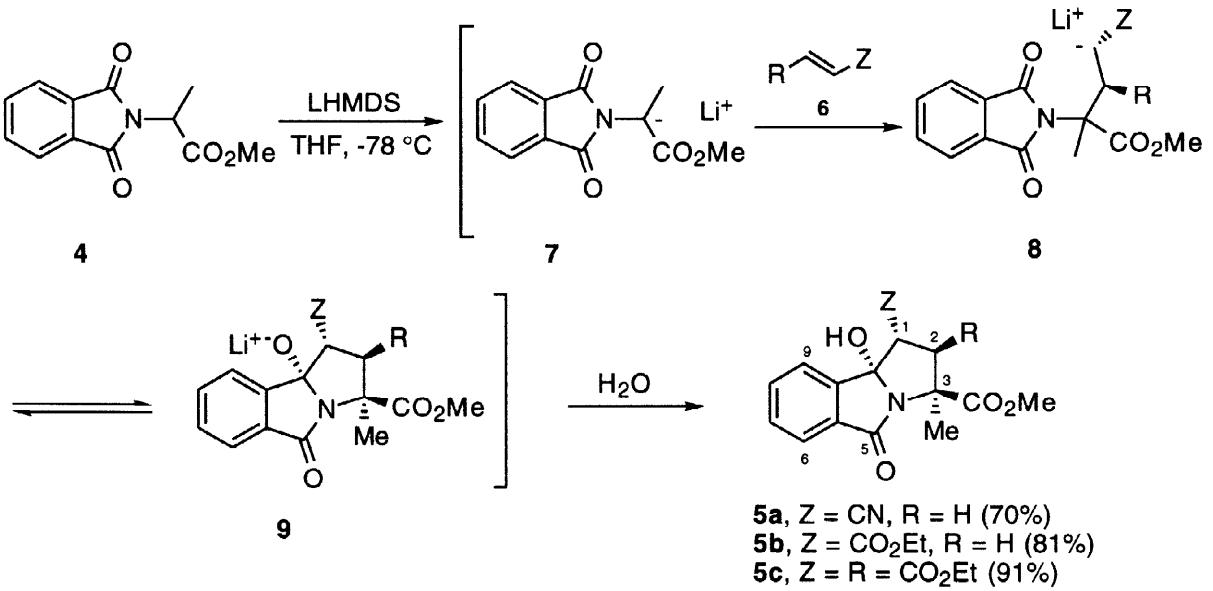
Scheme 1

In the course of our research program in the preparation and biological evaluation of thalidomide and analogs,[13] we undertook a study of functionalization of methyl (*dl*)-*N*-phthaloylalaninate (**4**). Herein we present a new stereoselective synthesis of 9b-hydroxy-5*H*-pyrrolo[2,1-*a*]isoindolo-5-ones **5a-5c**, based on a tandem Michael addition-intramolecular condensation[14] of **4** with unsaturated carboxyesters and cyano compounds **6** (Scheme 2).

RESULTS AND DISCUSSION

When racemic **4** is treated with lithium hexamethyldisilazide (LHMDS) at low temperature (-78 °C), carbanion **7** is formed, and it is expected to undergo 1,4-addition to α,β-unsaturated compounds, such as acrylonitrile (**6a**), ethyl acrylate (**6b**), and diethyl fumarate (**6c**). However, instead of producing the expected products of Michael addition, the pyrrolo[2,1-*a*]isoindolones **5a-5c** were obtained in high yields (Scheme 2). These compounds are presumably obtained through a sequence of reactions. Indeed, the conjugate addition of

anion **7** to unsaturated compound **6** should lead to the anionic intermediate **8**, that, by intramolecular addition to one of the carbonyl groups of the phthalimidyl moiety, gives rise to the observed products **5**.

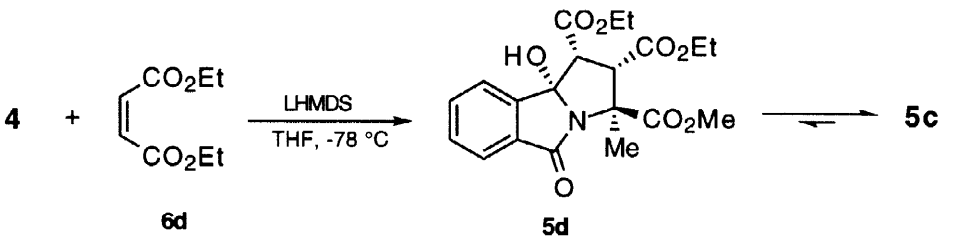


4 **7** **8** **9**

5a, Z = CN, R = H (70%)
5b, Z = CO_2Et, R = H (81%)
5c, Z = R = CO_2Et (91%)

Scheme 2

It is noteworthy that a single stereoisomer was formed, as confirmed by NMR of the crude mixtures. The relative configuration of the pyrrolidine ring was established by NOE experiments, and by X-ray crystallography. The ORTEP structures of **5a-5c** are depicted in Figure 1. The *trans* relative configuration of the ethoxycarbonyl groups on C-1 and C-2 of **5c** reveals that the *E* configuration of starting diethyl fumarate (**6c**) is retained during the formation of the anionic intermediate **8**, and its cyclization to **9**. Hence this reaction seems to be also stereospecific, a fact that may be supported by the evidence provided by ethyl maleate (**6d**). Indeed, **6d** undergoes addition of carbanion **7** at -78 °C (10 min) to give a mixture of pyrroloisoindolones **5c/5d** in a 25:75 ratio. This ratio did not change when the reaction was maintain for 1.5 h at the same temperature, whenever the quenching of the crude mixture takes place at -78 °C, otherwise the equilibrium is rapidly shifted toward the most stable C-2 epimer **5c** (Scheme 3). Moreover, a mixture of **5c/5d** in a >95:<5 ratio is obtained when the solvent is evaporated by warming up to 60 °C. Therefore, the **5c/5d** ratio may be readily modified by increasing the temperature, suggesting that the process is kinetically controlled.



6d **5d**

Scheme 3

The high stereoselectivity observed in the conversion of **4** to **5** may be rationalized in terms of the six-centered chairlike transition state model depicted in Figure 2, involving coordination between the two oxygen atoms, in the case of **6b** and **6c**, to the lithium ion.[15] The stereochemical control of the intramolecular condensation would depend on the relative stability of the two possible *Z* and *E* enolates, **A** and **B**.[16] The *Z* enolate **A**, which is expected to be the most stable *cis*-fused hydrindane type bicyclic transition state, would be preferred with respect to the sterically destabilized *E* enolate **B** (*trans*-fused hydrindane type bicycle). In the latter, gauche, and nonbonding van der Waals repulsive interactions would arise between the five-membered ring tether and the ethoxy group. Moreover, the *cis*-fused *Z* enolate **A** should be also preferred with respect to the *cis*-fused *E* enolate **C**, which might furnish the observed adducts as well. In transition state **C**, steric interactions between the ethoxy group and the substituent on carbon C-3 would destabilize it.

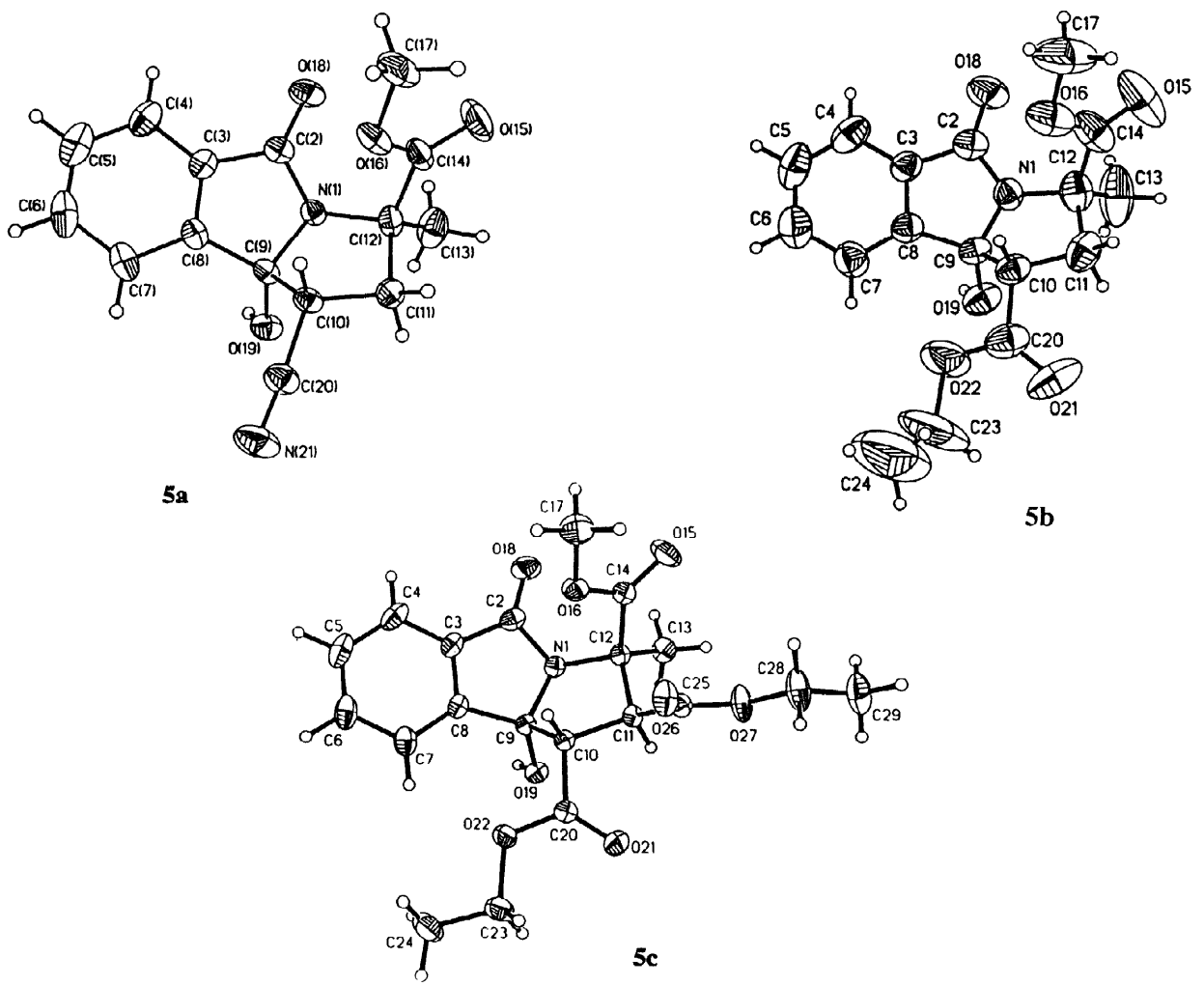


Figure 1. ORTEP structures of compound **5a**, one of the two conformational isomers of **5b** (the other molecule has an almost identical conformation), and **5c**.

This model would also account for the stereochemistry of substituents on carbon C-3, since in the *cis*-fused conformation **A** the small group (Me) is directed towards the concave face of the bicyclic transition state framework, whilst the methoxycarbonyl group remains in the less crowded convex face of the transition state.

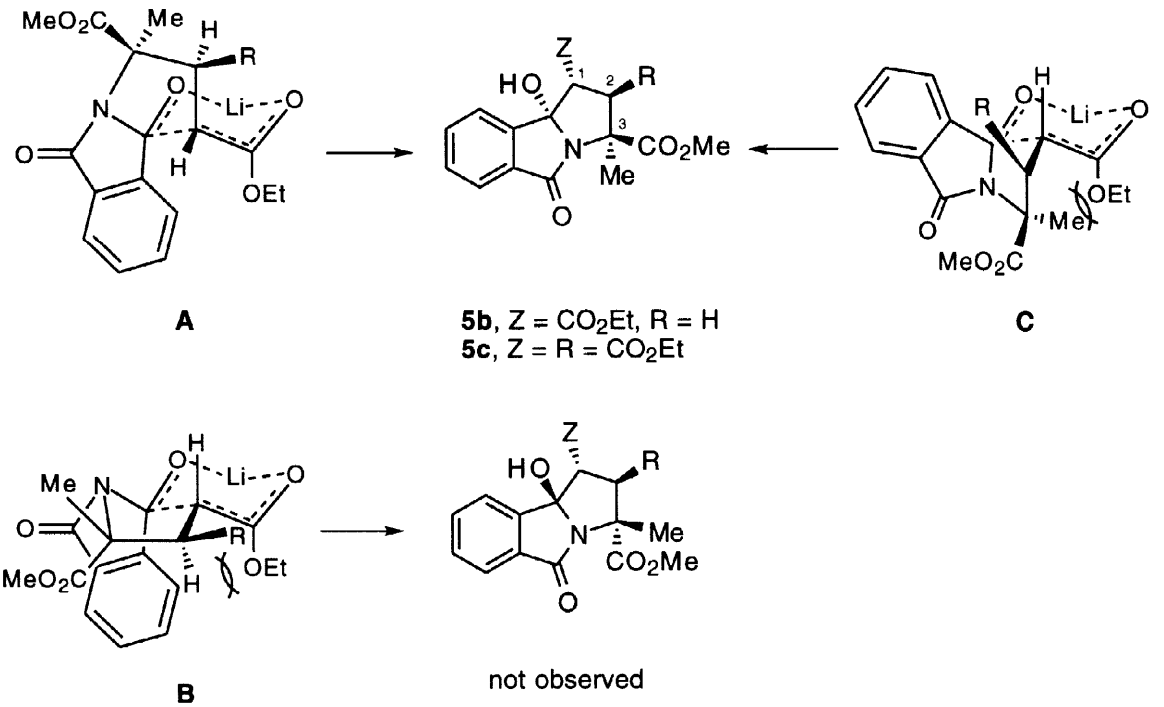


Figure 2.

That kinetic control of the stereochemistry takes place in this sequential process was further supported by experiments carried out at higher temperature (Table 1). When the addition of ethyl acrylate (**6b**) and the reaction were done at -78 °C for a short time, only **5b** was detected by NMR of the crude mixture (entry 1). At longer reaction times at the same temperature, a slow epimerization of **5b** towards **5e** was observed (Scheme 4). The amount of the latter increased when the temperature was risen to 0 °C, still within short ranges of time (entry 3), and significant isomerization resulted by increasing the temperature and reaction time (entries 4 and 5).

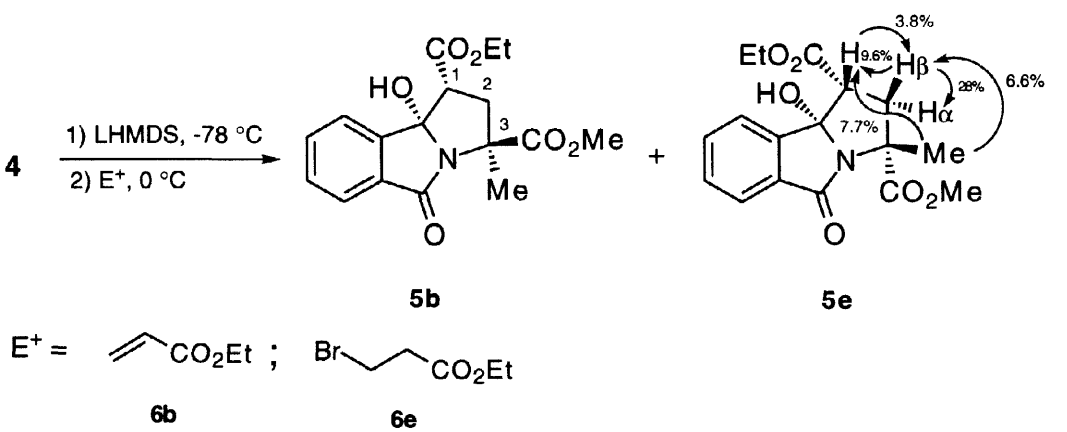
We also investigated the effect of the electrophile on the isomeric ratio. Thus, when ethyl β-bromopropionate (**6e**) was added at -78 °C, the reaction yielded a mixture of **5b/5e** (77:33) (Table 1, entry 6). Under the same conditions, but stopping the reaction after 1 h, the ratio was reversed (entry 7), in contrast with the trial using **6b** as the electrophile (see entry 2). It seemed likely, that the isomer ratio would be effected by the presence of LiBr in the reaction medium. To test this, the reactions were monitored by NMR within very short ranges of time. Thus, under the conditions of entry 6, up to 9% of ethyl acrylate (**6b**) was formed; while for the reaction starting with half the molar equivalents of **6e** (entry 8), the ratio **6b/6e** reached *ca.* 1:1, probably

liberating a higher concentration of bromide ion. On the other hand, when the lithium ion was increased, by furnishing a twofold equivalent of the base, the effect seems not to be significant, since the ratio **5b/5d** was comparable (*ca.* 12% of **6b** was detected, entry 9) with that recorded for stoichiometric amounts of base and starting materials (entry 6). These observations suggest that bromide ions are perturbing the assistance of the lithium ion on the stereocontrol of the cyclization step.

Table 1. Addition reactions of **4** to electrophiles **6b** and **6e**.[a]

Entry	E^+ (mol equiv)	T (°C) addition	T (°C) reaction	Time[b]	Products (ratio)[c]	Yield (%)[d]
1	**6b** (1.1)	-78	-78	5 min	**5e**	86 (81)
2	**6b** (1.1)	-78	-78	1 h	**5b/5e** (>95:<5)	80 (78)
3	**6b** (1.1)	-78	-78	5 min		
			0	15 min	**5b/5e** (83:17)	64 (60)
4	**6b** (1.1)	-78	-78	2 h		
			25	2 h	**5b/5e** (47:53)	32 (30)
5	**6b** (1.1)	-78	-78	6 h		
			25	15 h	**5b/5e** (30:70)	46 (42)
6	**6e** (1.1)	-78	-78	5 min	**5b/5e** (77:23)	40 (37)
7	**6e** (1.1)	-78	-78	1 h	**5b/5e** (28:72)	81 (76)
8	**6e** (0.5)	-78	-78	5 min	**5b/5e** (37:63)	50 (45)
9[e]	**6e** (1.1)	-78	-78	5 min	**5b/5e** (72:28)	33 (29)

[a] All under N_2 atmosphere, using LHMDS (1.04 mol equiv) for the anion generation of **4** in dry THF. [b] Reaction times at the temperature indicated. [c] Determined by ^1H NMR from the crude mixtures. [d] Total yield, and in the parenthesis after column chromatography and/or recrystallization. [e] 2.0 mol equiv of LHMDS.



Scheme 4

Stereoisomers **5b** and **5e** were separated by flash column chromatography. They were easily distinguishable by ^1H NMR, showing similar coupling patterns and chemical shifts for the H-1 and H-2 protons of the pyrrolidine ring. The experimental coupling constants agreed with values calculated by means of the Altona program (Table 2).[17] This suggests a similar pyrrolidine ring conformation in both molecules, which would be

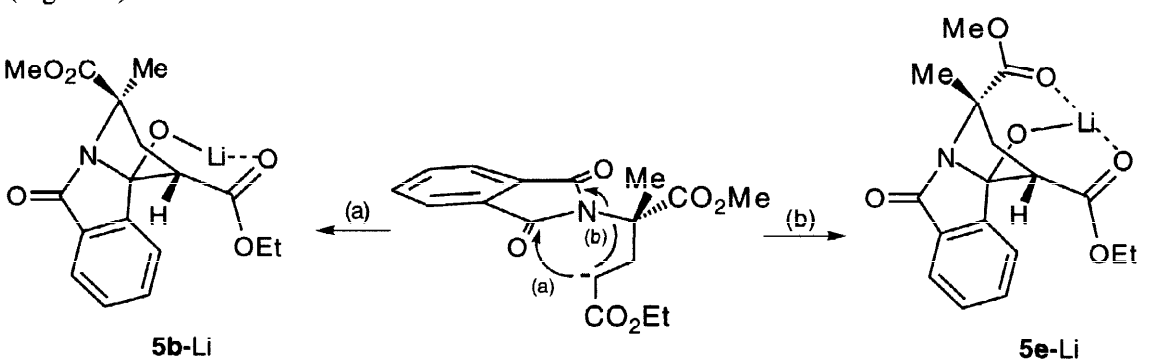
maintained as long as the *syn* relationship of the OH-9b and the ethoxycarbonyl group on C-1 is also preserved. However, a reversal of the chemical shifts of the *anti* protons H-1 and H-2α was determined between the two isomers. Therefore, carbon C-3 seems to be the epimeric center, and the structure of isomer **5e** would be that shown in Scheme 4. This assignement was supported by NOE experiments. The enhancement observed in the signals attributed to protons H-1 and H-2β, when the methyl group on C-3 was irradiated, indicates their *syn* spatial proximity (Scheme 4).

Table 2. ^{1}H NMR and Calculated Spectral Data of the Pyrrolidinic Ring of Compounds **5a**, **5b**, **5c**, **5d**, and **5e**.[a]

Compd[b]	δ (H-1)[c]	δ (H-2α)	δ (H-2β)	*J* (H-1/H-2α)[d]	*J* (H-1/H-2α)[e]	*J* (H-1/H-2β)[d]	*J* (H-1/H-2β)[e]	*J* (H-2α/H-2β)[d]
5a	3.22	2.93	2.79	12.1	11.6	6.9	5.9	12.7
5b	3.39	2.96	2.71	12.0	11.2	7.3	6.5	13.8
5c	3.64	4.19		12.0	13.5			
5d	3.45		4.51			11.7	9.0[f]	
5e	3.02	3.38	2.56	12.3		7.6		13.2

[a] Spectra were determined in deuteriochloroform. [b] Data of compounds **5a**, **5b**, and **5d** were collected at 270 MHz, and of compounds **5c** and **5e** at 300 MHz. [c] Chemical shifts in ppm and are relative to Me_4Si (δ = 0.0). [d] Experimental in Hz. [e] Calculated with the Altona program,[17] using the torsional angles given by the X-ray structures. [f] Calculated with the Altona program using torsional angles from a structure optimized by AM1.

Density functional (RB3LYP/6-31+G*//RHF/3-21G) calculations of both lithium chelated species **5b**-Li and **5e**-Li revealed that the latter is more stable by 7.16 kcal/mol (Figure 3). It appears that this greater stability is due to a supplementary complexation of the lithium ion by the C-3 carboxymethyl group, leading to the isomerization at carbon C-3 at the stage of the conjugate addition when the reaction is carried out to higher temperature, before the cyclization takes place. However, a more suitable epimerization outcome may be proposed by intramolecular addition of the carbanion to either one of the carbonyl groups of the phthalimidyl moiety or to the other: Path (a) would lead to the less stable chelate **5b**-Li; while path (b) would give rise to the more stable **5e**-Li (Figure 3).



5b-Li

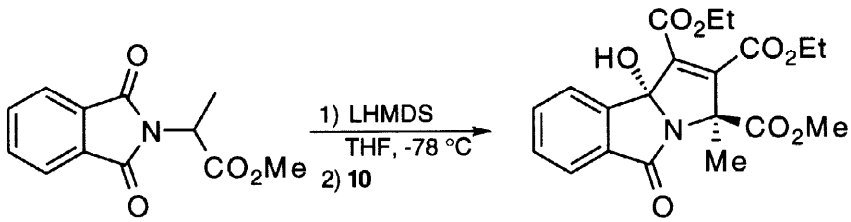
E = - 1133.09794670 au

5e-Li

E = - 1133.10936381 au

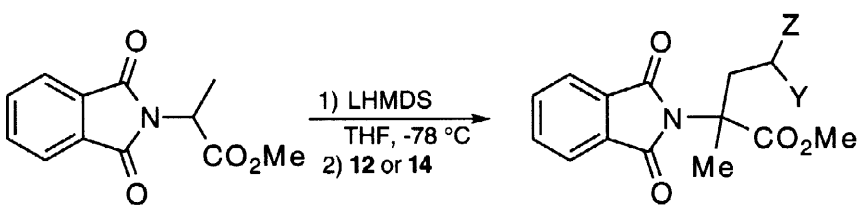
Figure 3

In order to evaluate the strain created by a double bond in the cyclization process, we investigated the addition of diethyl acetylenecarboxylate (**10**) (Equation 1). The reaction provided the cyclization adduct **11** in 83% yield. Once again, a single isomer was detected, showing that the process was highly stereoselective. Unfortunately, crystals of this product were not suitable for X-ray analysis. Assuming a similar conformational preference in the intramolecular addition, one could expect that the C-3 methyl group would be *syn* to the C-9b hydroxyl group as well.



4 **11**

To explore this tandem methodology further, other substituted olefins with different electron withdrawing groups were investigated. When phtalimide **4** was treated with methyl vinyl ketone (**12**) under similar conditions of base and low temperature, sole addition product **13** was isolated in 96% yield, and characterized by NMR. No cyclization product was detected in the crude mixture, even when the addition of **12** took place at -78 °C and the reaction was warmed up to room temperature. Under these conditions, partial decomposition of both starting material and product **13** was observed. Analogous behavior was observed with di-*t*-butyl methylenemalonate (**14**). The reaction provided a crude product containing a mixture of conjugate addition compound **15** and unreacted starting material in a 6:4 ratio, respectively (Equation 2).



4

13, Z = COMe, Y = H
15, Z = Y = CO_2t-Bu

The absence of intramolecular cyclization in these examples could be the result of an overstabilization of the carbanion intermediate by the electron-withdrawing groups. Steric hindrance could be anticipated for olefin **14**, as an additional factor preventing the cyclization.

In summary, we have shown a new approach for the stereoselective preparation of 5*H*-pyrrolo[2,1-*a*]isoindol-5-ones. This synthetic methodology consisted in a sequential Michael addition of the *in situ* generated anion of methyl *N*-phthalimidoalaninate (**4**) onto a series of unsaturated compounds, and cyclization of the

resultant anion intermediate by condensation with one of the carbonyl imido groups. Kinetic stereocontrol in the last step was supported by epimerization of carbon C-3 when the reaction was carried out at higher temperature. Methyl vinyl ketone (**12**) and di-*t*-butyl methylenemalonate (**14**) underwent conjugate addition but not intramolecular cycloaddition. Further experiments are currently underway in an attempt to gain additional insight into the structural and conformational requirements of the process.

EXPERIMENTAL SECTION

General. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 16F PC spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on Varian Gemini-300 (300 MHz), JEOL GSX-270 (270 MHz) and JEOL Eclipse-400 (400 MHz) instruments, with $CDCl_3$ as solvent and TMS as internal standard. The mass spectra (MS) were taken on a Hewlett-Packard 5989AMS spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and by Galbraith Laboratories, Knoxville, TN. THF was distilled from Na prior to use, and all other reagents were used without further purification.

Methyl DL-N-Phthaloylalaninate (4). To a solution of 7.35 g (50 mmol) of phthalimide in dry THF (50 mL) at room temperature, 7.6 g (50 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-eno (DBU) were added. After 10 min of stirring, 8.35 g (50 mmol) of methyl (±)-2-bromopropionate were added, and the mixture was stirred at room temperature for 2 h. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 25 mL). The organic layer was washed with a 10% aqueous solution of HCl (20 mL), a 5% aqueous solution of NaOH (20 mL), and brine (2 x 25 mL), and dried (Na_2SO_4). The solvent was removed in vacuo. The amorphous crystals were recrystallized from methanol, to yield 9.23 g (79%) of **4** as a colorless powder: mp 65-67 °C (lit.[18] mp 66-67 °C). ^1H NMR (270 MHz, $CDCl_3$) δ 1.70 (d, J = 7.4 Hz, 3H, Me-3), 3.75 (s, 3H, CO_2Me), 4.99 (q, J = 7.4 Hz, 1H, $NC\underline{H}CO_2Me$), 7.72-7.78 (m, 2H, ArH), 7.84-7.90 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 15.3 (Me), 47.4 (NCH), 52.8 ($CO_2\underline{C}H_3$), 123.5 (2C, ArH), 131.9 (2C, Ar), 134.2 (2C, ArH), 167.4 (2C, CON), 170.2 ($\underline{C}O_2Me$).

Di-tert-Butyl methylenemalonate (14). In 100 mL round-bottomed flask with condenser, and under a nitrogen atmosphere, 2.8 g (0.093 mol) of paraformaldehyde, 10.0 g (0.046 mol) of di-*tert*-butyl malonate, 0.47 g (2.37 mmol) of cupric acetate monohydrate, 0.46 g (4.75 mmol) of potassium acetate, and 20 mL of glacial acetic acid were mixed at room temperature. The mixture was stirred and heated to 100 °C for 2 h. The acetic acid was removed at reduced pressure (0.7 mmHg) first at room temperature, then at 100 °C. The residue was distilled in a Kugelrohr apparatus at a temperature range of 110-140 °C (0.3 mmHg). The distilled product was dissolved

in ether (20 mL) and washed with a 5% aqueous solution of $NaHCO_3$ (2 x 10 mL). The aqueous layer was extracted with ether (2 x 20 mL), and the organic extracts were mixed. and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was distilled in the Kugelrohr apparatus, collecting the product in a temperature range of 110-120 °C (0.3 mmHg) (lit[19] bp 82 °C/0.1 mmHg), to give 2.33 g (42%) of **14** as a colorless oil.

Refined Coordinates for the X-ray Crystallographic Data of Compounds 5a, 5b, and 5c are Summarized in Table 3.[20]

Table 3. Crystallographic Data for **5a**, **5b**, and **5c**.

	5a	**5b**[a]	**5c**
Formula	$C_{15}H_{14}N_2O_4$	$C_{17}H_{19}NO_6$	$C_{20}H_{23}NO_8$
Mw	286.28	333.33	405.39
Cryst. syst.	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/n$
Cryst. dimens, mm	0.18 x 0.28 x 0.78	0.2 x 0.4 x 0.6	0.33 x 0.22 x 0.14
a, Å	13.4411 (9)	18.530 (3)	7.8090 (1)
b, Å	11.8685 (10)	18.233 (2)	20.510 (2)
c, Å	9.1385 (10)	9.420 (2)	12.3970 (1)
V, Å^3	1418.0 (2)	3176.3 (9)	1985.5 (4)
α, deg	90	90	90
β, deg	103.415 (7)	93.611 (13)	90.440
γ, deg	90	90	90
λ, Å	0.71073	0.71073	0.71073
Z	4	8	4
F(000)	600	1408	856
μ, mm^{-1}	0.099	0.106	0.106
D (calc), g cm^{-3}	1.341	1.394	1.356
temp, °K	293 (2)	293 (2)	293 (2)
Diffractometer	Siemens P4	Siemens P4	Enraf Nonius CAD4
Radiation	Mo	Mo	Mo
Monochromator	graphite	graphite	graphite
2θ scan range, deg	3.12 to 52.00	4.40 to 52.00	5.16 to 49.94
No. of rflns collected	3664	7893	3758
No. of unique obsvd rflns	2793	6242	2084
R	0.0484	0.0727	0.0421
Rw	0.0867	0.1805	0.1160
Goodness of fit, on F^2	1.042	0.998	1.042
Largest residual peak (e Å^{-3})	0.153	0.246	0.293

[a] The unit cell is formed by two conformational isomers.

General Procedure for the Preparation of pyrrolo[2,1-a]isoindoles 5a-5c. To a solution of 1.165 g (5.0 mmol) of **4** in dry THF (20 mL), under an N_2 atmosphere at -78 °C, 6.33 mL (5.2 mmol, 1 M in THF) of LHMDS was added dropwise. The mixture was stirred at the same temperature for 1 h, and the electrophile **6a**, **6b**, or **6c** (5.0 mmol) was slowly added. The mixture was stirred for 1.5 h more, then a saturated solution of NH_4Cl (3 mL) was poured in. At room temperature, water was added (20 mL) and the product extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 7:3) to give:

(1R*,3R*,9bR*)-Methyl 1-Cyano-2,3,5,9b-tetrahydro-9b-hydroxy-3-methyl-5-oxo-1H-pyrrolo[2,1-a]isoindole-3-carboxylate (5a). 1.0 g (70%) of **5a** as colorless crystals (hexane/EtOAc, 2:1): R_f 0.23 (hexane/EtOAc, 7:3); mp 210-212 °C; IR (KBr) 2250, 1770, 1705 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.69 (s, 3H, Me-3), 2.79 (dd, *J* = 12.7, 6.9 Hz, 1H, H-2β), 2.93 (dd, *J* = 12.7, 12.1 Hz, 1H, H-2α), 3.22 (dd, *J* = 12.1, 6.9 Hz, 1H, H-1), 3.64 (s, 3H, CO_2Me), 4.15 (br s, 1H, OH), 7.47-7.74 (m, 4H, ArH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.5 (Me-3), 35.9 (C-2), 44.9 (C-1), 53.0 ($CO_2\underline{C}H_3$), 62.6 (C-3), 94.8 (C-9b), 116.6 (CN), 122.8 (C-9), 124.4 (C-6), 131.0 (C-7), 131.4 (C-5a), 133.8 (C-8), 143.9 (C-9a), 168.2 (C-5), 172.0 ($\underline{C}O_2Me$); MS (70 eV) 286 (M^+, 0.1), 269 (0.3), 255 (0.1), 227 (56), 209 (100), 181 (17), 130 (7), 104 (12), 76 (12). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 63.03; H, 5.08; N, 9.63.

(1R*,3R*,9bR*)-Methyl 1-Carboxyethyl-2,3,5,9b-tetrahydro-9b-hydroxy-3-methyl-5-oxo-1H-pyrrolo[2,1-a]isoindole-3-carboxylate (5b). After addition of **6b**, the mixture was stirred at -78 °C for 5 min, to give 1.30 g (86%) of **5b** as colorless crystals (hexane/EtOAc, 7:3): R_f 0.36 (hexane/EtOAc, 1:1); mp 152-153 °C; IR (KBr) 3418, 3384, 1748, 1732, 1718, 1704, 1695, 1682, 1468 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.78 (s, 3H, Me-3), 2.71 (dd, *J* = 13.8, 7.3 Hz, 1H, H-2β), 2.96 (dd, *J* = 13.8, 12.0 Hz, 1H, H-2α), 3.39 (dd, *J* = 12.0, 7.3 Hz, 1H, H-1), 3.68 (s, 3H, CO_2Me), 4.00 (s, 1H, OH), 4.24-4.42 (m, 2H, $CO_2C\underline{H}_2CH_3$), 7.48-7.54 (m, *J* = 7.3 Hz, 1H, ArH), 7.58-7.64 (m, *J* = 7.3 Hz, 1H, ArH), 7.67-7.73 (m, *J* = 7.3 Hz, 1H, ArH), 7.78-7.84 (m, *J* = 7.3 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 ($CO_2CH_2\underline{C}H_3$), 24.7 (Me-3), 43.4 (C-2), 49.1 (C-1), 52.5 ($CO_2\underline{C}H_3$), 61.5 ($CO_2\underline{C}H_2CH_3$), 62.2 (C-3), 95.5 (C-9b), 123.7 (C-6 or C-9), 123.9 (C-9 or C-6), 130.1 (C-7 or C-8), 132.1 (C-5a), 133.0 (C-8 or C-7), 145.6 (C-9a), 168.3 (C-5), 170.0 ($\underline{C}O_2Et$), 172.8 ($\underline{C}O_2Me$); MS (70 eV) 315 (M^+-H_2O, 1), 274 (55), 228 (95), 200 (100), 184 (26), 130 (35), 104 (35), 76 (33). Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 60.98; H, 5.90; N, 4.27.

(1R*,2R*,3R*,9bR*)-Methyl 1,2-Dicarboxyethyl-2,3,5,9b-tetrahydro-9b-hydroxy-3-methyl-5-oxo-1H-pyrrolo[2,1-a]isoindole-3-carboxylate (5c). 1.85 g (91%) of colorless crystals (hexane/EtOAc, 7:3) of **5c**: R_f 0.24 (hexane/EtOAc, 7:3); mp 146-147 °C; IR (KBr) 3443, 1750, 1732, 1718,

1709, 1407 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H, C-2/$CO_2CH_2C\underline{H}_3$), 1.38 (t, J = 7.1 Hz, 3H, C-1/$CO_2CH_2C\underline{H}_3$), 1.90 (s, 3H, Me-3), 3.58 (s, 3H, CO_2Me), 3.60 (s, 1H, OH), 3.64 (d, J = 12.0 Hz, 1H, H-1), 4.07-4.18 (m, 2H, C-2/$CO_2C\underline{H}_2CH_3$), 4.19 (d, J = 12.0 Hz, 1H, H-2), 4.26-4.42 (m, 2H, C-1/$CO_2C\underline{H}_2CH_3$), 7.46-7.52 (m, 1H, ArH), 7.59-7.65 (m, 2H, ArH), 7.78-7.88 (m, 1H, ArH); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.9 (C-2/$CO_2CH_2\underline{C}H_3$), 14.1 (C-1/$CO_2CH_2\underline{C}H_3$), 25.0 (Me-3), 51.4 (C-1 or C-2), 52.3 ($CO_2\underline{C}H_3$), 58.7 (C-2 or C-1), 61.3 (C-1/ and C-2/$CO_2\underline{C}H_2CH_3$), 64.6 (C-3), 94.2 (C-9b), 123.7, 124.0, 130.1, 131.4 (C-5a), 133.2, 145.4 (C-9a), 168.4, 168.5, 169.3, 170.1; MS (70 eV) 405 (M^+, 0.1), 388 (0.3), 346 (40), 328 (30), 300 (29), 254 (45), 226 (30), 104 (17), 76 (13), 29 (100). Anal. Calcd for $C_{20}H_{23}NO_8$: C, 59.25; H, 5.72; N, 3.45. Found: C, 59.18; H, 5.69; N, 3.49.

(1R*, 2S*, 3R*, 9bR*)-Methyl 1,2-Dicarboxyethyl-2,3,5,9b-tetrahydro-9b-hydroxy-3-methyl-5-oxo-1H-pyrrolo[2,1-a]isoindole-3-carboxylate (5d). To a solution of 0.72 g (3.1 mmol) of **4** in dry THF (15 mL), under an N_2 atmosphere at -78 °C, 3.92 mL (3.22 mmol, 1 M in THF) of LHMDS was added dropwise. The mixture was stirred at the same temperature for 1 h, and 0.5 mL (5.0 mmol) of **6d** was slowly added. The mixture was stirred for 1.5 h more, and maintaining the same temperature (-78 °C) a saturated solution of NH_4Cl (20 mL) was poured in, and the mixture was vigorously stirred, then EtOAc (20 mL) was added. The organic layer was promptly washed with cold water (2 x 20 mL), dried (Na_2SO_4), and the solvent was removed in high vacuum at < 10 °C, to give 1.2 g of crude. This was purified by radial chromatography (hexane/EtOAc/CH_2Cl_2, 70:15:15) to yield 0.165 g (23%) of **4**, 0.21 (17%) of **5c** [R_f 0.26 (hexane/EtOAc/CH_2Cl_2, 70:15:15 x 8)], and 0.66 g (53%) of **5d** [R_f 0.22 (hexane/EtOAc/CH_2Cl_2, 70:15:15 x 8)] as colorless powder. Data of **5d**: mp 138-140 °C; IR ($CHCl_3$) 3430, 1750-1700, 1460, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.37 (t, J = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.70 (s, 3H, Me-3), 3.45 (d, J = 11.7 Hz, 1H, H-1), 3.69 (s, 1H, OH), 3.89 (s, 3H, CO_2Me), 4.17-4.28 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.28-4.40 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.51 (d, J = 11.7 Hz, 1H, H-2), 7.49-7.54 (m, 1H, ArH), 7.58-7.64 (m, 1H, ArH), 7.70 (d, J = 7.7 Hz, 1H, ArH), 7.87 (d, J = 7.7 Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 ($CO_2CH_2\underline{C}H_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 29.7 (Me-3), 52.3, 53.5, 57.1, 61.6, 61.8, 63.7, 94.3, 123.8, 124.0, 130.3, 132.2, 133.1, 144.4, 166.2, 168.0, 169.2, 173.3; HRMS (FAB): calcd for [M^++1] $C_{20}H_{24}NO_8$: 406.1502. Found: 406.1538.

(1R*, 3S*, 9bR*)-Methyl 1-Carboxyethyl-2,3,5,9b-tetrahydro-9b-hydroxy-3-methyl-5-oxo-1H-pyrrolo[2,1-a]isoindole-3-carboxylate (5e). After addition of **6e**, the mixture was stirred at -78 °C for 6 h, then warmed up to room temperature for 15 h. The crude, containing a mixture of **5b/5e** (30:70), was purified by flash column chromatography on silica gel (hexane/EtOAc, 7:3), to give 0.2 g (12%) of **5b** and 0.51 g (31%) of **5e** as colorless powder (hexane/EtOAc, 7:3). Data of **5e**: R_f 0.28 (hexane/EtOAc, 1:1); mp 137-138

°C; IR (KBr) 3482, 1748, 1740, 1736, 1732, 1694, 1682, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.81 (s, 3H, Me-3), 2.56 (dd, *J* = 13.2, 7.6 Hz, 1H, H-2β), 3.02 (dd, *J* = 12.3, 7.6 Hz, 1H, H-1), 3.38 (dd, *J* = 13.2, 12.3 Hz, 1H, H-2α), 3.80 (s, 3H, CO_2Me), 3.93 (s, 1H, OH), 4.25-4.41 (m, 2H, $CO_2C\underline{H}_2CH_3$), 7.50 (td, *J* = 7.5, 1.1 Hz, 1H, ArH), 7.59 (td, *J* = 7.5, 1.3 Hz, 1H, ArH), 7.71 (dm, *J* = 7.5 Hz, 1H, ArH), 7.82 (dm, *J* = 7.5 Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.2 ($CO_2CH_2\underline{C}H_3$), 21.1 (Me-3), 43.5 (C-2), 49.2 (C-1), 53.1 ($CO_2\underline{C}H_3$), 61.5 ($CO_2\underline{C}H_2CH_3$), 62.4 (C-3), 96.0 (C-9b), 123.6 (C-6 or C-9), 123.7 (C-9 or C-6), 130.0 (C-7 or C-8), 132.6 (C-5a), 132.8 (C-8 or C-7), 144.7 (C-9a), 166.3 (C-5), 169.2 ($\underline{C}O_2Et$), 174.3 ($\underline{C}O_2Me$); MS (70 eV) 333 (M^+, 0.2), 302 (0.4), 274 (57), 228 (89), 200 (100), 184 (4), 172 (17), 130 (24), 104 (22), 76 (12). Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.74; N, 4.20. Found: C, 61.07; H, 5.66; N, 4.16.

(3R*,9bR*)-Methyl 1,2-Dicarboxyethyl-3,9b-dihydro-9b-hydroxy-3-methyl-5H-pyrrolo[2,1-a]isoindol-5-one-3-carboxylate (11). To a solution of 2.33 g (10.0 mmol) of **4** in dry THF (30 mL), under an N_2 atmosphere at -78 °C, 13.4 mL (11.0 mmol, 1 M in THF) of LHMDS was added dropwise. The mixture was stirred at the same temperature for 1 h, and 1.7 g (10.0 mmol) of **10** was slowly added. The mixture was still stirred for 1 h, then a saturated solution of NH_4Cl (10 mL) was poured in. At room temperature, water was added (20 mL) and the product extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The crude (3.65 g) was purified by recrystallization (EtOAc) to give 3.34 g (83%) of **11** as colorless crystals: R_f 0.20 (hexane/EtOAc, 7:3); mp 164-165 °C; IR (KBr) 3264, 1762, 1732, 1687, 1655, 1469 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.31 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.83 (s, 3H, Me-3), 3.58 (s, 3H, CO_2Me), 4.18 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.31 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.45 (s, 1H, OH), 7.40-7.49 (m, 1H, ArH), 7.52-7.65 (m, 2H, ArH), 7.66-7.72 (m, 1H, ArH); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.9 ($CO_2CH_2\underline{C}H_3$), 14.0 ($CO_2CH_2\underline{C}H_3$), 23.3 (Me-3), 52.9 ($CO_2\underline{C}H_3$), 62.1 ($CO_2\underline{C}H_2CH_3$), 62.3 ($CO_2\underline{C}H_2CH_3$), 70.4 (C-3), 99.3 (C-9b), 124.2, 124.5, 130.5, 131.7 (C-5a), 133.7, 136.7, 144.2, 144.7, 161.5, 162.6, 168.0, 169.6; MS (70 eV) 386 (M^+-H_2O, 1), 344 (45), 298 (100), 226 (27). Anal. Calcd for $C_{20}H_{21}NO_8$: C, 59.54; H, 5.24; N, 3.47. Found: C, 59.64; H, 5.28; N, 3.41.

Methyl 2-Methyl-5-oxo-2-phthalimidohexanoate (13). To a solution of 1.165 g (5.0 mmol) of **4** in dry THF (20 mL), under an N_2 atmosphere at -78 °C, 6.33 mL (5.2 mmol, 1 M in THF) of LHMDS was added dropwise. The mixture was stirred at the same temperature for 1 h, and 0.35 g (5.0 mmol) of **12** was slowly added. The mixture was still stirred for 1 h, then a saturated solution of NH_4Cl (3 mL) was poured in. At room temperature, water was added (20 mL) and the product extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The crude (1.6 g) was purified by flash column chromatography on silica gel (hexane/EtOAc, 7:3) to give 1.45 g (96%) of **13** as pale yellow oil: R_f

0.43 (hexane/EtOAc, 7:3); IR (KBr) 1780, 1748, 1724, 1714 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.83 (s, 3H, Me-2), 2.10 (s, 3H, COMe), 2.48-2.66 (m, 4H, CH_2CH_2), 3.74 (s, 3H, CO_2Me), 7.71-7.86 (m, 4H, ArH); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 22.3 (Me-2), 29.3 ($\underline{C}H_3CO$), 29.1 (CH_2), 38.2 (CH_2), 52.2 ($CO_2\underline{C}H_3$), 62.1 (C-2), 123.2 (2C, ArH), 131.6 (2C, Ar), 134.3 (2C, ArH), 168.6 (2C, CON), 172.5 ($\underline{C}O_2CH_3$), 207.5 ($\underline{C}OCH_3$); MS (70 eV) 303 (M^+, 0.5), 260 (3), 244 (37), 200 (16), 148 (47), 97 (100). Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.51; H, 5.85; N, 4.42.

ω-tert-Butyl, α-Methyl 4-Carboxy-tert-butyl-2-Methyl-N-phthaloylglutamate (15). To a solution of 1.5 g (6.4 mmol) of **4** in dry THF (20 mL), under an N_2 atmosphere at -78 °C, 8.52 mL (7.0 mmol, 1 M in THF) of LHMDS was added dropwise. The mixture was stirred at the same temperature for 1 h, and 1.0 g (4.4 mmol) of **14** was slowly added. The mixture was still stirred for 2 h, then at 0 °C for 1 h. A saturated solution of NH_4Cl (3 mL) was poured in. At room temperature, water was added (20 mL) and the product extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The crude (1.62 g) was purified by by flash column chromatography on silica gel (hexane/CH_2Cl_2, 1:1) to give 0.96 g (47%) of **15** as an amorphous semisolid: R_f 0.43 (hexane/EtOAc, 7:3); IR ($CHCl_3$) 1780, 1744, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H, *t*-Bu), 1.32 (s, 9H, *t*-Bu), 1.86 (s, 3H, Me-2), 2.63 (dd, J = 15.0, 4.7 Hz, 1H, CH_2), 2.78 (dd, J = 15.0, 6.4 Hz, 1H, CH_2), 3.40 (dd, J = 6.4, 4.7 Hz, 1H, CH), 7.64-7.80 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8 (Me-2), 27.6 ($CO_2C(\underline{C}H_3)_3$), 27.7 ($CO_2C(\underline{C}H_3)_3$), 34.2 ($CH_2$), 49.8 (CH), 52.7 ($CO_2\underline{C}H_3$), 62.1 (C-2), 81.5 ($CO_2\underline{C}(CH_3)_3$), 81.6 ($CO_2\underline{C}(CH_3)_3$), 123.1 (2C, ArH), 131.8 (2C, Ar), 134.0 (2C, ArH), 168.3, 168.4, 168.5, 172.3 ($\underline{C}O_2CH_3$). Anal. Calcd for $C_{24}H_{31}NO_8$: C, 62.46; H, 6.77; N, 3.03. Found: C, 62.50; H, 6.78; N, 3.03.

***Ab initio* Calculations.** The *ab initio* calculations were carried out with the Gaussian 94 package.[21] Structures **5b**-Li and **5e**-Li were fully optimized at the RHF/3-21G level of theory, and characterized by frequency analysis at the same level. Single point calculations at the RB3LYP/6-31G(d) calculations were then carried out on these structures.

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REFERENCES AND NOTES

1. For a review: Coyle, J. D. *Phthalimide and Its Derivatives*, in *Synthetic Organic Photochemistry*, Horspool, W. M., Ed.; Plenum Press: New York, 1984; pp 259-284.
2. Griesbeck, A. G. *Liebigs Ann.* **1996**, 1951. Easton, C.; Hutton, C. A. *Synlett* **1998**, 457.
3. (a) Lee, Y. J.; Lee, C. P.; Jeon, Y. T.; Mariano, P. S.; Yoon, U. C.; Kim, D. U.; Kim, J. C.; Lee, J. G. *Tetrahedron Lett.* **1993**, *34*, 5855. (b) Yoon, U. C.; Kim, D. U.; Kim, J. C.; Lee, J. G.; Mariano, P. S.;

Lee, Y. J.; Ammon, H. L. *Tetrahedron Lett.* **1993**, *34*, 5859. (c) Yoon, U. C.; Oh, S. W.; Lee, C. W. *Heterocycles* **1995**, *41*, 2665. (d) Takahashi, Y.; Miyashi, T.; Yoon, U. C.; Oh, S. W.; Mancheno, M.; Su, Z.; Falvey, D. F.; Mariano, P. S. *J. Am. Chem. Soc.* **1999**, *121*, 3926.

4. Close, M.; Coyle, J. D.; Haws, E. J.; Perry, C. J. *J. Chem. Res. (S)* **1997**, 6681, and references cited therein.
5. Hatanaka, Y.; Sato, Y.; Nakai, H.; Wada, M.; Mizoguchi, T.; Kanaoka, Y. *Liebigs Ann.* **1992**, 1113.
6. Maruyama, K.; Kubo, Y. *J. Org. Chem.* **1981**, *46*, 3612.
7. Yavari, I; Islami, M. R. *J. Chem. Res. (S)* **1998**, 714.
8. Minami, T.; Watanabe, K.; Hirakawa, K. *Chem. Lett.* **1986**, 2027.
9. Nudelman, A.; Marcovici, D.; Nachum, A. *Heterocycles* **1994**, *38*, 751.
10. Grishakov, A. N.; Matveeva, T. V.; Krasnov, V. P.; *Russ. J. Org.* **1998**, *34*, 357.
11. Griesbeck, A. G.; Henz, A.; Kramer, W.; Lex, J.; Nerowski, F.; Oelgemöller, M.; Peters, K.; Peters, E.-M. *Helv. Chim. Acta* **1997**, *80*, 912. Griesbeck, A. G.; Henz, A.; Hirt, J. *Synthesis* **1996**, 1261. See also: Bullington, J. L.; Dodd, J. H. *J. Heterocyclic Chem.* **1998**, *35*, 397.
12. Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M.; Urzúa, A. *Tetrahedron* **1984**, *40*, 3957.
13. (a) Santos-Mendoza, T.; Favila-Castillo, L.; Oltra, A.; Tamariz, J.; Labarrios, F.; Estrada-Parra, S.; Estrada-García, I. *Int. Arch. Allergy Inmunol.* **1996**, *111*, 13. (b) Fragoso, M., B.Sc. Thesis, Fac. Est. Sup. Zaragoza, UNAM (Mexico), 1993. (c) De Paz, G., B.Sc. Thesis, Esc. Nal. Ciencias Biológicas, IPN (Mexico), 1996.
14. For previous reports of Michael-induced ring closures, see: (a) Posner, G. H.; *Chem. Rev.* **1986**, *86*, 831. (b) Little, R. D.; Verhé, R.; Monte, W. T.; Nugent, S.; Dawson, J. R. *J. Org. Chem.* **1982**, *47*, 362. (c) Yechezkel, T.; Ghera, E.; Ramesh, N. G.; Hassner, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2423.
15. (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Stereoselective Aldol Condensations*, in *Topics in Stereochemistry*, Allinger, N. L.; Eliel, E. L.; Wilen, S. H., Eds.; John Wiley & Sons: New York, 1982; Vol 13, pp 1-115. (b) Heathcock, C. H. *Stereoselective Aldol Condensation*, in *Comprehensive Carbanion Chemistry*, Buncel, E.; Durst, T., Eds.; Elsevier: Amsterdam, 1984, Part B, p. 177. (c) Oare, D. A.; Heathcock, C. H. *Stereochemistry of the Base-Promoted Michael Addition Reaction*, in *Topics in Stereochemistry*, Eliel, E. L.; Wilen, S. H., Eds.; John Wiley & Sons: New York, 1989; Vol 19, pp 227-407. (d) T. Mukaiyama, *Org. Reactions* **1982**, *28*, 203.
16. Formation of the *Z* enolates is favored when the disilazide bases are used, or when the substrate possesses bulky α'-substituents: Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.
17 Cerda-García-Rojas, C. M.; Zepeda, L. G.; Joseph-Nathan, P. *Tetrahedron Comp. Method.* **1990**, *3*, 113.
18. Caswell, L. R.; Campbell, R. D. *J. Chem. Soc.* **1961**, 4175.
19. Ballesteros, P.; Roberts, B. W.; Wong, J. *J. Org. Chem.* **1983**, *48*, 3603.

20. The atomic coordinates for these structures are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
21. Gaussian 94, Revision E.2, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.