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β-Amino Acids to Piperidinones by Petasis Methylenation and Acid-Induced Cyclization

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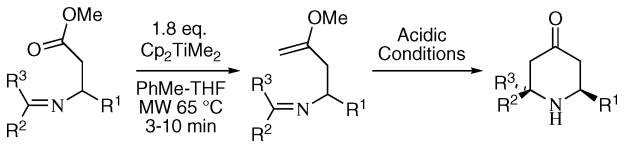
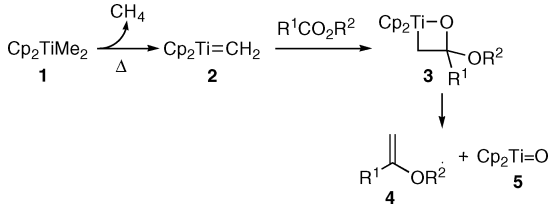


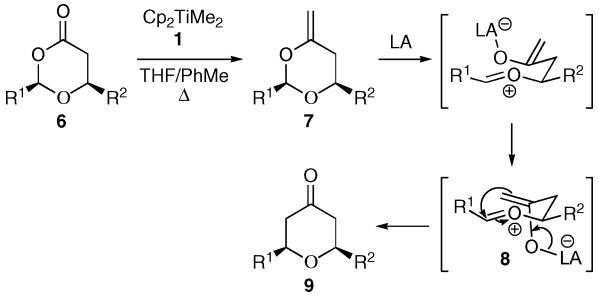
Ester-imine derivatives of β-amino acids were methylenated with dimethyltitanocene under microwave irradiation and the resulting enol ethers cyclized with Brönsted acid or triisopropylaluminium to give 2,6-*syn*-disubstituted piperidinones in good yield and diastereoselectivity. The method is analogous to the Petasis−Ferrier rearrangement of 1,3-dioxan-4-ones to give tetrahydropyranones.

Titanium carbenoids are useful reagents for converting carbonyl groups into alkenes because they are small and nonbasic, but above all because they will convert carboxylic acid derivatives into the corresponding hetero-substituted alkenes.[1] A range of titanium carbenoids have been used to methylenate esters,[2,3] but the reagent used by Petasis, dimethyltitanocene (DMT) **1**, has particular advantages: it is easy to prepare and handle and is not strongly Lewis acidic, and the workup following reaction often involves simple precipitation of the titanium-containing side products.[4] Indeed, DMT has been used to methylenate an ester on a 235 Kg scale [with recycling of the titanocene by precipitation as $(Cp_2TiMe)_2O$, conversion to Cp_2TiCl_2 with HCl, and regeneration with MeLi].[5] The active titanocene methylidene **2** is generated thermally via α-elimination[6] and this reacts with esters to give oxatitanacylcobutane intermediates **3**,[7] which collapse to give the enol ethers **4** and oxotitanocene **5** (Scheme 1).

SCHEME 1. Methylenation of Esters



SCHEME 2. Petasis−Ferrier Rearrangement



One application of DMT **1** is in the Petasis−Ferrier rearrangement,[8] which has been shown by Smith and co-workers[9] to be an exceptionally powerful tool for the total synthesis of complex natural products. It involves methylenation of a 1,3-dioxan-4-one **6** with DMT **1** to give an enol ether **7**, which rearranges under Lewis-acidic conditions to give a 2,6-*syn*-disubstituted tetrahydropyranone **9** via oxonium ion **8** (Scheme 2). Surprisingly, the nitrogen analogue of this rearrangement, which would be expected to provide a diastereoselective route to piperidinones, has not been reported.

Concise stereocontrolled routes to piperidines are of interest,[10−12] as this moiety is considered to be a privileged structure[13] for the discovery of new drug compounds. Perhaps the best known 2,6-disubstitued piperidene alkaloids are the spiropiperidine, histrionicotoxin **10**,[14] which is a potent nicotinic receptor antagonist and lobeline **11**,[15] which has been used to treat nicotine addiction (Figure 1).

For our route to piperidinones, we reasoned that chemoselective methylenation of the ester group of an imino-ester **12** might be possible using DMT **1** (Scheme 3), because the titanium atom in titanium methylidene **2** is oxophilic and the driving force for reaction is the formation of the strong titanium−oxygen double bond of oxotitanocene **5**. Treatment of the resulting enol ether **13** with a Brönsted acid would generate an intermediate **14**, which is analogous to the oxonium ion **8** involved in the Petasis−Ferrier rearrangement. This should cyclize to give oxonium ion **15**, which would be further protonated to give ammonium salt **16** (or eliminated to give a related enol ether), which upon hydrolysis would yield piperidinone **17**. Similar intramolecular Mannich reactions between enols or enol ethers and iminium ions have been shown to give good 2,6-*syn* selectivity.[11]

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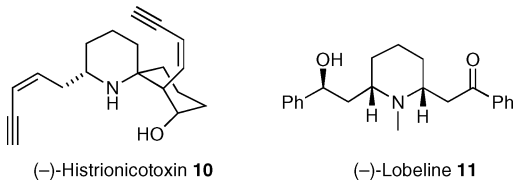
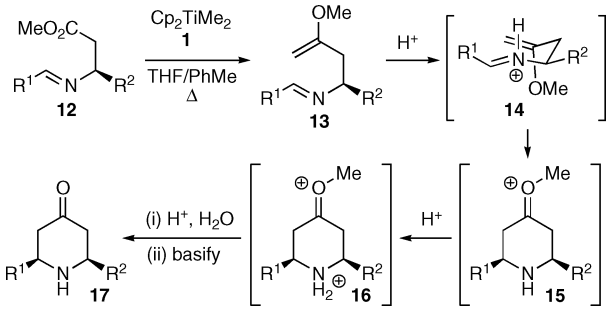


FIGURE 1. 2,6-Disbstituted piperidine alkaloids.

The route began from the commercially available racemic β-amino acids, which were converted into their methyl esters **18** in 98−100% yield by using thionyl chloride in methanol. Imines **19A**−**C** and **19E**−**K** of aldehydes were then prepared at room temperature with sodium sulfate as desiccant,[16] while imines **19D** and **19L** derived from ketones were prepared by using azeotropic removal of water (Scheme 4 and Table 1).[17] DMT **1** was prepared by Payack's method as a 1.3 M solution in THF−toluene (1:1), which could be stored at 4 °C.[4] Methylenation of the esters **19** was carried out in sealed tubes under microwave irradiation,[18,19] allowing very short reaction times and clean conversion to enol ethers **20**. Initially, reaction

SCHEME 3. Proposed Route to Piperidinones



mixtures were heated to 80 °C with 100 W microwave power and the temperature maintained for 10 min, but later we found that heating to 65 °C (approximately 7 min) and maintaining this temperature for 10 min was sufficient. Indeed, even these mild conditions were too harsh for electron-rich imines **19C**, **F**, and **G** and enaminizable imine **J**. For these, the pressure was monitored and when it ceased to rise, after only 3 min at 65 °C, the reaction was stopped because we reasoned that production of methane by α-elimination was complete. This shorter reaction time gave clean conversion. Clearly, the control allowed by using microwave heating is key to the success of the transformations. It is significant that the temperature is no higher than that employed in conventionally heated Petasis methylenations, but the reaction time is substantially shorter than those normally reported. After precipitation of the titanium-containing residues with hexane, complete reaction of the esters **19** was confirmed by ^{1}H NMR spectroscopy of the crude mixtures[20] and the sensitive enol ethers **20** were used immediately, without further purification.

Initially, aqueous acid was used to combine the cyclization and hydrolysis steps in Scheme 3. A range of concentrations of aqueous HCl were investigated (2.4−12 M), and 7 M proved optimum at ensuring hydrolysis occurred after cyclization, but not before cyclization. This procedure was effective for piperidinones **21A** and **21B** derived from the imines **19A** and **19B** of benzaldehyde, and can be viewed as an environmentally benign procedure since it uses no organic solvents (entries 1 and 2, Table 1). Only the 2,6-*syn* diastereomer was observed in each case. However, the method was not general and was poor-yielding for electron-rich imine **20C** and ketone-derived imine **20D** (entries 3 and 4). Presumably, in these cases cyclization is slower and hydrolysis of the imine and enol ether groups competes.

Using two equivalents of tosic acid under anhydrous conditions in chlorinated solvents overcomes this problem to some extent. Again, derivatives of benzaldehyde give good yields of piperidinones (entries 5 and 6), as single *syn* isomers, following hydrolysis of the cyclized oxonium ions **16** in aqueous acid, followed by basification. Modest yields of 2,6-*syn* piperidinones **21C** and **21F**, derived from more electron-rich imines **20C** and **20F**, could also be obtained (entries 7 and 8). However, reaction was slower (sometimes requiring elevated temperature, entries 6 and 8) and was most conveniently carried out overnight. The efficiency of cyclization improved (compare entries 7 and 9) when using more polar solvents, DME and DMSO (entries

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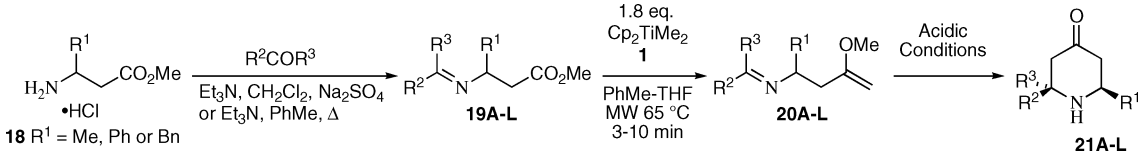
(20) The presence of the enol ether is confirmed by two broad 1H singlets in the range of 3.5−4.0 ppm in the ^{1}H NMR spectrum, and the signals for $CH_2C(OMe)=CH_2$ appear 0.2−0.3 ppm upfield from the signals for CH_2CO_2Me of the starting ester, so that complete conversion from starting material can be confirmed by ^{1}H NMR spectroscopy.

TABLE 1. Summary of Reaction Conditions and Yields for the Synthesis of Piperidinones

entry	compd	yield[a] of imine **19**, %	piperidinones **21**			cyclization conditions					yield[b] from **19**, %
			R^1	R^2	R^3	acid	solvent	temp, °C	time, h	hydrolysis	
1	**A**	75[c]	Me	Ph	H	7 M HCl	H_2O	20	0.5		61[d]
2	**B**	89	Ph	Ph	H	7 M HCl	H_2O	20	0.5		62[d]
3	**C**	94	Ph	2,4-$MeOC_6H_3$	H	7 M HCl	H_2O	20	17		12[d]
4	**D**	74[e]	Me	Ph	Me	7 M HCl	H_2O	20	17		trace
5	**A**	75[c]	Me	Ph	H	2 equiv of TsOH	CH_2Cl_2	20	17	1 M HCl (0.5 h)	61
6	**E**	83	$PhCH_2$	Ph	H	2 equiv of TsOH	CH_2Cl_2	40	17	1 M HCl (0.5 h)	61
7	**C**	94	Ph	2,4-$MeOC_6H_3$	H	2 equiv of TsOH	CH_2Cl_2	20	17	1 M HCl (0.5 h)	40
8	**F**	87[c]	Me	(*E*)-4-$MeOC_6H_4CH{=}CH$	H	2 equiv of TsOH	$CHCl_3$	60	17	1 M HCl (0.5 h)	37
9	**C**	94	Ph	2,4-$MeOC_6H_3$	H	2 eq.uiv of TsOH	DME	20	17	1 M HCl (0.5 h)	51
10	**G**	61	Me	2,4-$MeOC_6H_3$	H	2 equiv of TsOH	DME	20	17	1 M HCl (0.5 h)	58
11	**H**	58	Me	3-Br C_6H_4	H	2 equiv of TsOH	DME	20	17	1 M HCl (0.5 h)	48
12	**I**	90	Ph	^{t}Bu	H	2 equiv of TsOH	DME	20	17	1 M HCl (0.5 h)	58
13	**J**	91[f]	Ph	Et	H	2 equiv of TsOH	DME	20	17	1 M HCl (0.5 h)	34
14	**B**	72	Ph	Ph	H	2 equiv of TsOH	DMSO	28	17	1 M HCl (0.5 h)	61
15	**A**	75[c]	Me	Ph	H	2 equiv of Al(^{i}Bu)$_3$	DMSO	28	17	1 M HCl (0.5 h)	68
16	**B**	72	Ph	Ph	H	2 equiv of Al(^{i}Bu)$_3$	DMSO	28	17	1 M HCl (0.5 h)	70
17	**C**	94	Ph	2,4-$MeOC_6H_3$	H	2 equiv of Al(^{i}Bu)$_3$	DMSO	28	17	1 M HCl (0.5 h)	66
18	**K**	55	Me	2-F C_6H_4	H	2 equiv of Al(^{i}Bu)$_3$	DMSO	28	17	1 M HCl (0.5 h)	64
19	**F**	87[c]	Me	(*E*)-4-$MeOC_6H_4CH{=}CH$	H	2 equiv of Al(^{i}Bu)$_3$	DMSO	28	17	1 M HCl (0.5 h)	51
20	**D**	74[e]	Me	Ph	Me	2 equiv of Al(^{i}Bu)$_3$	DMSO	28	17	1 M HCl (0.5 h)	69[g]
21	**L**	73	Ph	$-(CH_2)_5-$		2 equiv of Al(^{i}Bu)$_3$	DMSO	28	17	1 M HCl (0.5 h)	52

[a] Isolated yield from amines **18** after purification. [b] Isolated yield after purification; except where otherwise indicated, only the 2,6-*syn* isomer was detected by NMR of the crude mixture and only this isomer was isolated; relative stereochemistry was assigned by NOE, except for **21B**, which was assigned by comparison with the literature. [c] Yield based on aldehyde. [d] Isolated as HCl salt. [e] *E*:*Z* ratio was 93:7. [f] **19**:**18**:propionaldehyde 80:13:7. [g] dr (2,6-*syn*:2,6-*anti*) = 89:11 in both crude mixture and isolated material.

SCHEME 4. Synthesis of Piperidinones



9−14), presumably because these, like water, can stabilize the developing positive charge of the oxonium ion **15** (Scheme 3). The imine derivatives **19J** and **20J** of propionaldehyde were unstable and difficult to handle, due to their propensity to form reactive enamine intermediates, and this accounts for the low yield of piperidinone **21J** (entry 13) compared to piperidinone **21I** (entry 12). Indeed, in spite of steric interactions, bulky imine **20I** cyclizes efficiently.

Petasis and co-workers had found that triisobutylaluminium at low temperature in toluene induced Ferrier rearrangement of vinyl acetals derived from 1,3-dioxan-4-ones, but that the resulting tetrahydropyranones were reduced under the reaction conditions to give 4-hydroxytetrahydropyrans.[8] We found that enol ethers **20** were cleanly converted into piperidinones **21** using this Lewis acid in DMSO, followed by hydrolysis in good yield and with excellent selectivity. The choice of such a polar solvent is unusual when using a Lewis acid, but reaction in dichloromethane was slower and led to the formation of complex mixtures. As before, we reason that stabilization of developing carbocation character in the transition state leading to a cyclized oxonium ion is important. No reduced product is observed because the ketone is only formed in the hydrolysis step and the oxygen atom in the oxonium ion intermediates is too poor a Lewis base to associate with the triisobutylaluminum in DMSO.

A range of imines cyclized well, including those derived from aromatic aldehydes (entries 15−18), an α,β-unsaturated aldehyde (entry 19), an alkyl aryl ketone (entry 20), and a dialkyl ketone (yielding a spirocyclic piperidine **21L**, entry 21). The Lewis acidic conditions are superior to those using protic acid, both for easily cyclized substrates (compare entries 1, 5, and 15) and for more demanding electron-rich imines (compare entries 3, 7, 9, and 17). The 2,6-*syn* isomers were the only products, except in the case of trisubstituted piperidinone **21D**, where the *syn*:*anti* ratio was 89:11, which was only a small decline on the *E*:*Z* ratio of the starting imines **19D**.

In summary, we report a highly diastereoselective route to 2,6-disubstituted piperidinones that is analogous to the Petasis−Ferrier rearrangement, having microwave-assisted Petasis methylenation and Lewis acid-induced cyclization as the key steps. This diastereoselective route should be applicable to the preparation of enantiopure piperidinones from enantiopure β-amino esters, which are straightforward to prepare.[21]

Experimental Section

Microwave-Assisted Petasis Methylenation. A 1.30 M solution of Cp_2TiMe_2 **1** (1.8−2.1 equiv) in toluene−THF (1:1 by mass) was added to an imino-ester **19** (1 equiv), and the solution was sealed in a 10 mL microwave tube under argon. This was irradiated under 100 W microwave power to raise the internal temperature to 65 °C (ca. 7 min), and the temperature was maintained with microwave irradiation for a further 2.5−10 min (the exact times and maximum internal pressures observed are included for individual transformations in the Supporting Information) before

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cooling. The resultant black solution was concentrated under reduced pressure and hexane added to precipitate most titanium-containing impurities. The hexane extract was filtered and concentrated under reduced pressure to yield the crude enol ether **20**, which was used directly in the cyclization reactions.

Lewis Acid-Induced Cyclization. Triisobutylaluminium (1.0 M in hexanes, 2 equiv) was added to the crude enol ether **20** (1 equiv, 0.03 M) in dry DMSO, under Ar. The solution was stirred at 28 °C for 17 h, and then quenched by careful addition of 1 M $HCl_{(aq)}$ (35 equiv). The reaction mixture was stirred for a further 45 min, then it was basified with $NaOH_{(aq)}$ and extracted with EtOAc. The organic extract was washed with $NH_4Cl_{(aq)}$, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude piperidinone **21**, which was purified by column chromatography.

Supporting Information Available: Full experimental procedures, spectroscopic data, and scanned ^1H NMR and ^{13}C NMR spectra for compounds **18** (Me, Ph and Bn), **19A**−**L** (with the exception of **19J**, which was unstable), and **21A**−**L**. This material is available free of charge via the Internet at http://pubs.acs.org.

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