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Direct-type vinylogous Mukaiyama–Michael addition reactions involving pyrrolinone donors

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ABSTRACT

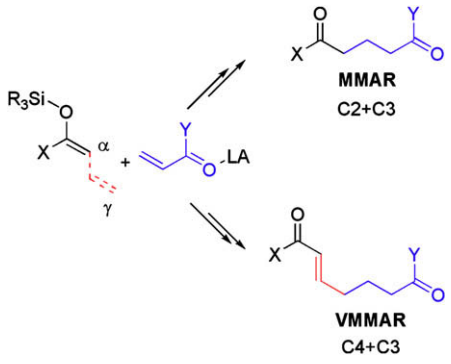
The direct Mukaiyama–Michael addition of vinylogous tetramate donors to a number of different Michael acceptors has been easily executed, by employing the TMSOTf/Et_3N mixture as soft Lewis acid/base promoter agent. Richly functionalized, highly manipulable γ-substituted pyrrolinone products were practically synthesized in acceptable to excellent yields, and with diastereoselectivities heavily relying upon the substituent at the nitrogen atom of the pyrrolinone donor.

1. Introduction

Since its very first appearance, the Mukaiyama–Michael aldol reaction (MMAR), that is, the 1,4-conjugate addition of enol silanes (or silyl ketene acetals) to Lewis acid-activated vinylogous carbonyl (or carboxyl-type) acceptors, excels as a preeminent synthetic methodology in the jurisdiction of the carbon–carbon bond-forming reactions (Scheme 1).[1] Even more appealing and less exploited is the vinylogous version of the reaction (VMMAR), where a conjugated silyl dienolate species couples to a Michael acceptor giving rise to useful α,β-unsaturated C4+C3 homologated 1,7-dicarbonyl compounds.[2]

In the vinylogous realm, Katsuki and colleagues documented the asymmetric Michael addition of 2-(trimethylsiloxy)furans to oxazolidinone enoates in the presence of BINOL-lanthanide or bis(oxazoline) Cu(II) triflate catalysts.[3] There, the use of preformed silyl dienolate donors and mild reaction conditions provided formation of the expected doubly vinylogous addition products, with complete chemo- and regiocontrol, and with moderate to high levels of diastereo- and enantioselectivity (e.g., Scheme 2, Eq. 1).[4] As a further elegant example, MacMillan and co-workers utilized the same furan-based silyldienolates in the first enantioselective organocatalytic vinylogous Mukaiyama–Michael addition to crotonaldehyde (Scheme 2, Eq. 2).[5] In that occasion, the imidazolidinone-based organocatalyst, while serving as the chiral activator of the electrophile through iminium ion formation, provided temporary protection of the aldehyde function, resulting in high enantioinduction and complete regiocontrol.[6]

In these and other examples of VMMAR,[7] a common operational modality is emphasized, according to which the reagent destined to become the donor species first undergoes a stoichiometric activation to give rise to a silyl dienolate, and the reagent destined to



Scheme 1. Conjugate addition of silyl enolate (MMAR) or silyl dienolate (VMMAR) donors to conjugated carbonyl acceptors. X, Y=H, R, OR, NR_2; LA=Lewis acid.

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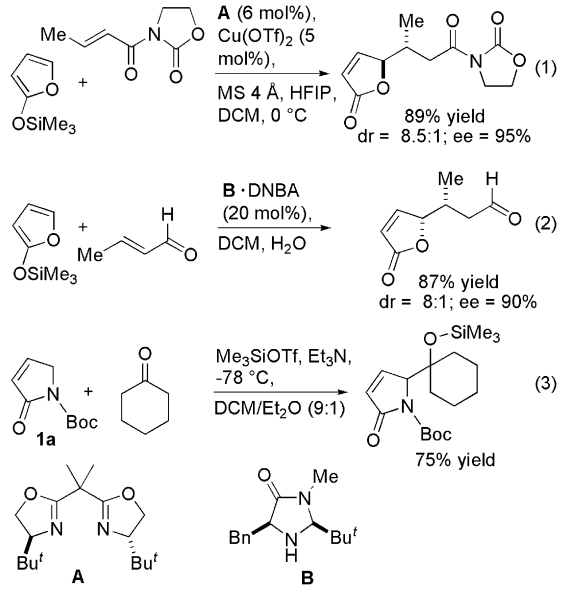


Scheme 2. Examples of indirect VMMAR (Eqs. 1 and 2) and direct vinylogous Mukaiyama aldol reaction (Eq. 3).

become the acceptor species is subjected to proper activation as well. An alternative, technically simplified modality would be especially desirable, where both unmodified partners are put in the same flask, while a suitable reagent or reagent mixture establishes their simultaneous in situ activation, while dictating the chemo-, regio- and stereoselectivity of the process. Direct, biomimetic routes have been indeed pursued in recent organic synthesis programmes, and development of direct-type aldol reactions using metal catalysts,[8] organocatalysts[9] and Bronsted or Lewis acid/base systems[10] has been the focus of intense research.

Our own contribution in the field encompasses the use of triethyl amine/trialkylsilyl triflate reagent couple in both the intramolecular direct and silylative aldolization reaction involving suitable aldehydo-lactams,[11] and in the intermolecular direct, silylative aldol addition of *N*-(*tert*-butoxycarbonyl)pyrrol-2(5*H*)-one (**1a**) to a number of aldehyde and ketone acceptors (e.g., Scheme 2, Eq. 3).[12]

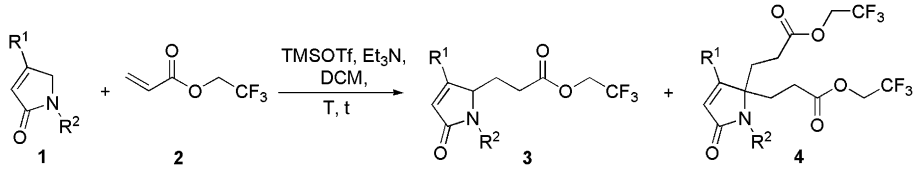
We now report that the Et_3N/TMSOTf reagent mixture is also adaptable for the direct and vinylogous Mukaiyama–Michael addition reaction. Specifically, selection of suitable pyrrolinone donors and their conjugate addition to a limited array of non-enolizable and enolizable Michael acceptors are here described in detail.

2. Results and discussion

We embarked on the present investigation to firmly probe the virtues of pyrrolin-2-one-based rings as easily available conjugated donors and to assess the properties of the TMSOTf/Et_3N couple as a soft activating mix during VMMAR. To begin, *N*-Boc-pyrrolinone **1a** was selected as the nucleophile component to be coupled to trifluoroethyl acrylate (**2**), a mildly activated ester electrophile. The addition of **1a** to **2** was carried out in the presence of TMSOTf/Et_3N reaction mixture (2.0:1.5 mol equiv) at −78 °C in dichloromethane (Table 1, entry 1), according to the optimized reaction conditions previously discovered in the aldol domain (vide supra).[12] In the event, complete absence of reactivity was observed, even when the reaction temperature was raised to 0 °C. An analogous trial using *N*-deprotected pyrrolinone **1b** (entry 2) proved unsuccessful, with almost complete recovery of untouched starting pyrrolinone.[13]

We reasoned that the intrinsically lower reactivity of conjugated ester electrophiles such as **2** as compared to that of carbonyl substrates would have been responsible for the observed apathy of **1a** or **1b** towards acrylate **2**, which instead would have required 'more activated' nucleophiles. Our attention thus turned to known compounds **1c**–**1e**, whose pyrrolin-2-one structure tightly resembles that of **1a**, **1b**, though the presence of an additional 4-methoxy substituent confers them increased reactivity. Indeed, the 4-alkoxytetramate ring is a well represented structural motif in the field of naturally occurring substances, many of which exhibiting attractive antibiotic and cytostatic activities.[14,15]

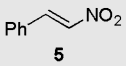
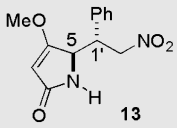
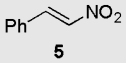
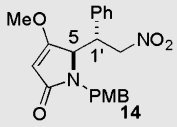
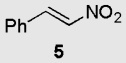
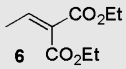
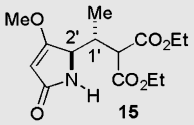
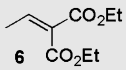
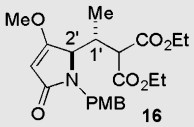
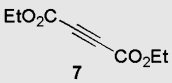
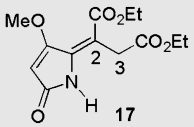
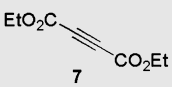
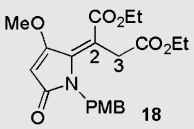
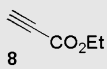
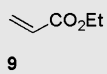
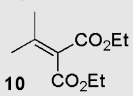
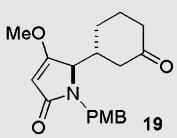
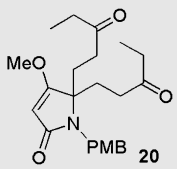
Table 1
Preparatory evaluation of VMMAR between pyrrolinone donors **1** and trifluoroethyl acrylate **2**[a]



Entry	Donor (R^1, R^2)	TMSOTf equiv	Et_3N equiv	*T* (°C)	*t* (h)	Product(s) (R^1, R^2),[b] yield %[c]	Recovered **1**[c] (%)
1	**1a** (H, Boc)	2.0	1.5	−78 to 0	12		96
2	**1b** (H, H)	2.0	2.0	−25	12		94
3	**1c** (OMe, H)	2.0	2.0	−40 to −25	12	**3c** (OMe, H), 10; **4c** (OMe, H), 36	35
4	**1c** (OMe, H)	2.0	2.0	−78	18	**3c** (OMe, H), 54; **4c** (OMe, H), 15	16
5[d]	**1c** (OMe, H)	2.0	2.0	−25	4	**4c** (OMe, H), 92	—
6	**1c** (OMe, H)	0.15	0.15	−30	12	**4c** (OMe, H), 13	75
7	**1c** (OMe, H)		2.0	22	12		93
8[e]	**1c** (OMe, H)		2.0	22	12		95
9	**1d** (OMe, Boc)	1.0	1.0	−78	12		94
10	**1d** (OMe, Boc)	1.0	1.0	−20	4		92
11	**1e** (OMe, PMB)	1.0	1.0	−78	12	**3e** (OMe, PMB), 15; **4e** (OMe, PMB), 15	65
12	**1e** (OMe, PMB)	1.0	1.0	−30	6	**3e** (OMe, PMB), 19; **4e** (OMe, PMB), 23	57
13[d]	**1e** (OMe, PMB)	1.0	1.0	−25	6	**4e** (OMe, PMB), 94	—

[a] Unless otherwise noted, the reactions were carried out in the presence of donor **1**/acceptor **2** (1.0/1.0 equiv), with the indicated equivalents of TMSOTf and Et_3N, with a substrate concentration of 0.4 M in DCM (0.26 mmol scale) at the indicated temperature under nitrogen atmosphere. Quenching conditions: H_2O and saturated aq NH_4Cl. For details, see Section 4.
[b] Products **3** are racemic substances.
[c] Isolated yield.
[d] Donor **1**/acceptor **2** (1.0/2.2 equiv).
[e] MeOH was used as the solvent.

Table 2
Scope of TMSOTf/Et_3N promoted VMMAR using tetramate donors **1c** and **1e**[a]

Entry	Donor	Acceptor	T (°C)	t (h)	Product(s)[b,c]	Yield[d] %	*anti*/*syn* ratio[e]
1	**1c**	 **5**	−78	8	 **13**	73	>13:1
2	**1e**	 **5**	−78	2	 **14**	70	1.4:1
3[f]	**1e**	 **5**	−78	8		[g]	
4	**1c**	 **6**	−78	12	 **15**	98	>30:1
5	**1e**	 **6**	−78	12	 **16**	64	2:1
6	**1c**	 **7**	−78	4	 **17**	83[h]	
7	**1e**	 **7**	−70	4	 **18**	37[g,i]	
8	**1c**	 **8**	−20	12		[g]	
9	**1c**	 **9**	−78 to 22	12		[g]	
10	**1c**	 **10**	−78 to 22	12		[g]	
11	**1c**	 **11**	−20 to 22	24		[g]	
12	**1e**	 **11**	−20	12	 **19**	90	1:0.8
13	**1e**	 **12**	22	12	 **20**	53[g,j]	

[a] Unless otherwise noted, the reactions were carried out in the presence of donor **1**/acceptor **2** (1.0/2.0 equiv), TMSOTf/Et_3N (2.0/2.0 equiv), with a substrate concentration of 0.4 M in DCM (0.26 mmol scale) at the indicated temperature under nitrogen atmosphere. Quenching conditions: H_2O and saturated aq NH_4Cl. For details, see Section 4.
[b] Except for derivatives **17**, **18**, and **20**, the indicated compounds are racemic substances.
[c] Major isomer reported (skeleton numbering according to IUPAC rules).
[d] Isolated, combined yield.
[e] Determined by ^1H NMR analysis of crude reaction mixtures.
[f] Only Et_3N used as the promoter.
[g] Starting pyrrolinone recovered.
[h] *E*-olefin geometry based on 2D NOESY experiments (see text).
[i] VMMAR product also obtained (30% isolated yield, *E*/*Z* 1.5:1).
[j] Mono-alkylated γ-isomer also obtained (17%).

When *N*-unprotected tetramate **1c** was subjected to the Et_3N/TMSOTf mixture (2.0:2.0 mol equiv, −40 to −25 °C, entry 3), the expected vinylogous Mukaiyama–Michael product **3c** was obtained in very scarce yield (10%), accompanied by considerable amounts of both the starting pyrrolinone (35%) and adduct **4c** (36%), coming from sequential double alkylation at the donor γ-position. By performing the reaction at lower temperature (−78 °C, entry 4) a reverted result was witnessed, with nice production of **3c** in a 54% isolated yield, and minor quantities of **4c** and **1c**. This indicated that competitive mono-γ- and bis-γ,γ- attacks could be partially controlled by the reaction temperature, and conditions to exclusive and high-yielding production of **4c** could be found by simply doubling the quantity of the acrylate component (entry 5).

Reaction between **1c** and **2** under catalytic conditions (TMSOTf/Et_3N 0.15:0.15 mol equiv, entry 6) afforded small quantities of **4c** exclusively (13%), with almost complete recovery of the starting reagent. This result showed that the silyl triflate and the tertiary amine do not regenerate during the reaction course, and smooth protonation and desilylation of the silyl ketene acetal from the Michael addition solely occurs just after the quenching procedure. With the use of triethyl amine alone at room temperature, reaction of **1c** with **2** completely failed, irrespective of the solvent used (aprotic vs protic, entry 7 vs 8). These experiments clearly demonstrated the crucial role displayed by the silicon Lewis acid in promoting the VMMAR process.[16]

Changing *N*-unsubstituted tetramate **1c** for the corresponding *N*-protected derivatives **1d** (*N*-Boc) and **1e** (*N*-*p*-methoxybenzyl) produced markedly different results: under almost the same reaction conditions (TMSOTf/Et_3N 1.0:1.0 mol equiv, −78 or −20/−30 °C, entries 9–13), **1d** proved a totally incompetent donor substrate, whilst **1e** gave the corresponding mono- and/or bis-alkylated products **3e**/**4e** in variable proportions, according to the reaction temperature and the equivalents of acrylate **2** employed (entries 11–13).

On the bases of these preliminary studies, we concluded that the dual TMSOTf/Et_3N promoting system could be able to trigger a direct VMMAR between pyrrolinone donors and acrylate **2**, provided that suitable tetramate rings of type **1c** and **1e** were used. Though not brilliant, the best results in Table 1 (entries 4, 5 and 13) prompted us to evaluate the scope of the reaction, by coupling **1c** and/or **1e** with a functionally diverse array of electrophilic partners. The results of this screening are displayed in Table 2.

Under optimized conditions, direct addition of tetramates **1c** or **1e** to β-nitrostyrene **5** gave easy entry to the expected VMMAR products **13** and **14** in good isolated yields (73% and 70%, respectively, entries 1 and 2) and with diastereoselectivities strictly depending upon the donor employed. Indeed, when *N*-deprotected pyrrolinone **1c** was used, a separable mixture of *anti*-**13** and *syn*-**13** was obtained, which displayed a pronounced diastereomeric bias (*anti*/*syn* ratio >13:1). The relative 5,1′-relative stereodisposition was unequivocally established by X-ray crystallographic determination of minor isomer *syn*-**13** (Fig. 1). When, instead, *N*-*p*-methoxybenzyl substituted donor **1e** was employed, a mixture of *syn* and *anti* isomers **14** was recovered, with only slight preponderance of the 5,1′-*anti* isomer. A plausible rationalization of these results is given below.

In spite of its high reactivity, nitroalkene **5** failed to couple to **1e** in the presence of the sole Et_3N base (entry 3), emphasizing, once again, the crucial, vicarious role displayed by the silicon Lewis acid/tertiary amine base couple in promoting the VMMAR process.

Enolizable ethylidene diethyl malonate **6** served as a superb electrophile, which directly coupled to **1c** or **1e** to afford the desired lactams **15** and **16** in high isolated yields, with no traces of self-condensation products (98% and 64%, entries 4 and 5). Again, the diastereoselectivity of the event heavily relied on the substituent at the donor nitrogen, with exclusive formation of 1′,2′ *anti*-configured

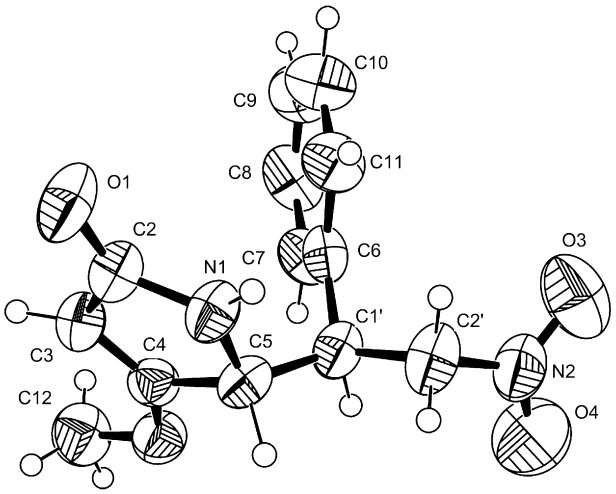


Figure 1. X-ray crystal structure of *syn*-**13** establishing its 5,1′-*syn* relative stereodisposition (ORTEP plot, 50% thermal ellipsoids).

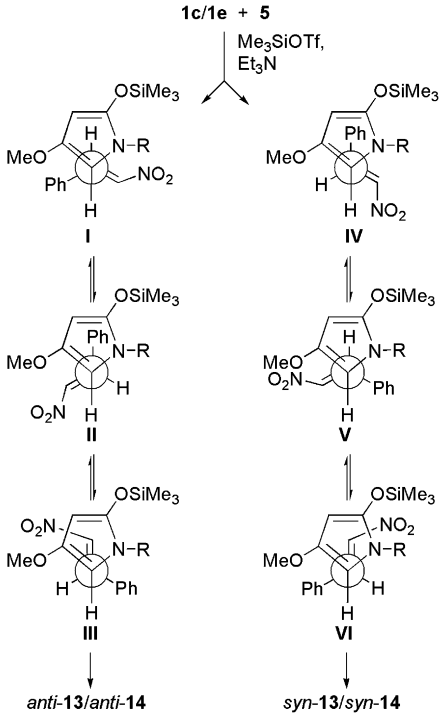
isomer *anti*-**15** in the first case, and a 2:1 mix of *anti*/*syn* adducts **16** in the latter, thus imitating the stereochemical behaviour reported above. The 5,1′-*anti* relative configuration of compound *anti*-**15**, as well as those of *syn*- and *anti*-**16**, were assigned mainly based on ^1H NMR spectral analogy to nitro-derivatives **13** and **14**.

With alkyne **7** as the Michael acceptor, pyrrolinone **1c** easily converted into the expected VMMAR product (as evidenced by TLC), but its isolation was precluded by rapid and complete transformation into highly conjugated alkylidene isomer **17** during silica gel flash chromatographic purification. The *E*-olefin geometry of compound **17** was unambiguously assigned based on 2D NOESY experiments, which revealed a diagnostic contact between pyrrolinone NH and H3 methylene protons. In case of reaction of **1e** with **7**, alkylidene product **18** could be isolated in a 37% yield, along with the expected VMMAR isomeric product (not shown) and unreacted starting pyrrolinone (see Section 4).

Other less reactive unsaturated esters such as ethyl propiolate **8** and ethyl acrylate **9**, or highly β-hindered malonate **10** were not able to react under the scrutinized conditions, and returned the starting tetramates **1c** and **1e** almost untouched (entries 8–10).

Finally, a couple of conjugated ketone electrophiles were selected, to assay the viability of the direct VMMAR procedure on carbonyl substrates. Thus, when enolizable cyclohexenone **11** was reacted with **1e**, smooth conversion into the Mukaiyama–Michael adduct **19** was witnessed (90% yield, entry 12), with only partial 5,1′-*anti* diastereo-preference, as usual. Astonishingly enough, however, tetramate **1c** was not able to couple to **11** under the guidance of the TMSOTf/Et_3N mixture, whichever the temperature conditions used (entry 11, see infra). Reaction of **1e** with acyclic ethyl vinyl ketone **12** afforded achiral bis-alkylated γ-adduct **20** as the major product, accompanied by minor amounts of a mono-γ-substituted product (not shown). In this instance, the behaviour of ketone **12** paralleled that of trifluoroethyl acrylate **2**, breaking the general trend followed by electrophiles in Table 2 where mono-γ-adducts were solely detected.[17]

While a precise rationale accounting for the observed diastereoselectivity awaits further study, we propose that with *N*-unsubstituted tetramate **1c**, a favourable, 'tight' transition state such as **I** may be invoked (Scheme 3, R=$SiMe_3$), where the silicon atom from the Lewis acid connecting to the vacant pyrrolinone nitrogen[13] coordinates (or electronically interacts) to the oxygen atom of the electron-withdrawing group of the Michael acceptor (e.g., nitro-, carboxylate-, carbonyl-group). Analogous tight interaction such as in transition state conformer **VI** would seem less favourable, thus



Scheme 3. The Newman projections of possible transition state conformers **I**-**VI** during VMMAR homologations of **1c** (R=$SiMe_3$) or **1e** (R=PMB) to β-nitrostyrene **5**.

explaining preferential formation of *anti*-configured compounds (e.g., *anti*-**13**, *anti*-**15**) over the respective *syn*-isomers, when tetramate **1c** is used. On the other hand, the presence of the *p*-methoxybenzyl group within **1e** would impede formation of such cyclic transition states, and competitive open chain models (e.g., **II** and **IV**, R=PMB) could be almost equally operative, thus resulting in poor diastereocontrol (e.g., compounds **14** and **16**).[18]

3. Conclusion

In summary, it was possible to introduce a succinct methodology for the vinylogous Mukaiyama–Michael reaction in a direct modality by selecting a couple of especially functionalized pyrrolinone conjugated donors (e.g., **1c** and **1e**) and by utilizing the well-tested TMSOTf/Et_3N promoter pair. This method could be successfully applied to an array of differently functionalized vinylogous acceptors as nitro-olefins, α,β-unsaturated esters and conjugated ketones, allowing easy entry to γ-substituted 2-pyrrolinone products, whose plain functional decoration renders them high calibre intermediary compounds.

According to a very easy technical execution, where donor, acceptor, and promoter couple are mixed together without the use of sophisticated manoeuvres or ultra-delicate reagent systems, the expected doubly vinylogous addition products were obtained in acceptable to useful yields and diastereoselectivities strongly relying upon the substituent at the pyrrolinone nitrogen. In limited cases, the reaction failed or provided concurrent bis-alkylation products.

With these premises in hands, development of the present study towards an asymmetric domain is felt as desirable further step, and results in this field will be reported soon.

4. Experimental section

4.1. General

Organic solvents were dried and freshly distilled before use according to the literature procedures. Reactions were generally run under a nitrogen atmosphere. TLC analysis was performed on silica gel 60 F_{254} plates with visualization under short-wavelength UV light or by dipping the plates with molybdate reagent (aq H_2SO_4 solution of cerium sulfate/ammonium molybdate) followed by heating. Flash chromatography was performed on 40–63 μm silica gel using the indicated solvent mixtures. Melting points were determined with an optical thermomicroscope and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300/75 MHz at 22 °C unless otherwise noted. Chemical shifts (δ) are given in parts per million (ppm) using chloroform-*d* or DMSO-d_6 as internal references. Detailed peak assignments were performed using conventional 1D and 2D NMR experiments, such as COSY, NOESY, HMQC and DEPT sequences.

4.2. Materials

1-(*tert*-Butoxycarbonyl)-1*H*-pyrrol-2(5*H*)-one (**1a**) and 1*H*-pyrrol-2(5*H*)-one (**1b**) were prepared from pyrrole according to a reported procedure.[12] 4-Methoxy-1*H*-pyrrol-2(5*H*)-one (**1c**) and 1-(4-methoxybenzyl)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**1e**) were prepared from condensation of commercial methyl (*E*)-4-chloro-3-methoxy-2-butenoate and 10% aq ammonia or commercial *p*-methoxybenzylamine, respectively (75% and 64% yields), according to reported procedures.[19] Compound **1c** is also commercially available. 1-(*tert*-Butoxycarbonyl)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**1d**) was prepared from **1c** using the standard $(Boc)_2O$/DMAP conditions (98% yield). 2,2,2-Trifluoroethyl acrylate (**2**), 1-[(*E*)-2-nitrovinyl]benzene (**5**), diethyl 2-ethylidenemalonate (**6**), diethyl but-2-ynedioate (**7**), ethyl propiolate (**8**), ethyl acrylate (**9**), diethyl 2-(propan-2-ylidene)malonate (**10**), cyclohex-2-enone (**11**), and pent-1-en-3-one (**12**) were commercially available and used as such without further purification.

4.3. Experimental procedures and compounds characterization

*4.3.1. Representative procedure for the vinylogous Mukaiyama–Michael addition reaction (VMMAR) between pyrrolinones **1** and Michael acceptors: preparation of 2,2,2-trifluoroethyl 3-[(2R*)-2,5-dihydro-3-methoxy-5-oxo-1H-pyrrol-2-yl]propanoate (**3c**) and bis(2,2,2-trifluoroethyl) 3,3′-(2,5-dihydro-3-methoxy-5-oxo-1H-pyrrole-2,2-diyl)dipropanoate (**4c**) (Table 1, entry 4)*

To a solution of pyrrolinone **1c** (30 mg, 0.265 mmol) in dry dichloromethane (DCM, 0.7 mL), kept under a nitrogen atmosphere, were sequentially added triethyl amine (Et_3N, 74 μL, 0.53 mmol) and trimethylsilyloxytriflate (TMSOTf, 97 μL, 0.53 mmol). The resulting pale yellow solution was stirred for 10 min at room temperature and then cooled to −78 °C. After stirring at −78 °C for 10 min, 2,2,2-trifluoroethyl acrylate (**2**) (34 μL, 0.265 mmol) was added dropwise and the resulting solution was stirred at the same temperature for 18 h. Water (2 mL) was then added at −78 °C and, after stirring for 10 min, saturated aq NH_4Cl solution (3 mL) was added. The resulting mixture was allowed to warm to room temperature (22 °C) and transferred to a separatory funnel. The aqueous layer was separated and extracted with DCM (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellowish oil, which was purified by silica gel flash chromatography (DCM/MeOH 95:5) to afford compound **3c** (38.2 mg, 54% yield), compound **4c** (16.7 mg, 15% yield), as well as recovered **1c** (4.8 mg, 16%). Data for **3c**: a white solid; mp 106–108 °C; IR (neat) ν_{max} 2933, 1753, 1674, 1621, 1282, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (br s, 1H, NH), 5.06 (d, *J*=0.8 Hz, 1H, H4′), 4.51 (dq, *J*=12.6, 8.5 Hz, 1H, CH_2CF_3), 4.45 (dq, *J*=12.6, 8.2 Hz, 1H, CH_2CF_3), 4.18 (t, *J*=5.4 Hz, 1H, H2′), 3.82 (s, 3H, OMe), 2.52 (ddd, *J*=17.6, 8.9, 7.1 Hz, 1H, H2), 2.43 (ddd, *J*=17.6, 8.7, 6.1 Hz, 1H, H2), 2.10–2.20 (m, 1H, H3), 1.90–

2.05 (m, 1H, H3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.3 (Cq, C5′), 174.5 (Cq, C3′), 171.3 (Cq, C1), 122.0 (q, $^1J_{C,F}$=275 Hz, Cq, *C*F$_3$), 94.2 (CH, C4′), 60.4 (q, $^2J_{C,F}$=36 Hz, CH_2, O*C*H$_2$CF$_3$), 58.4 (CH_3, OMe), 56.2 (CH, C2′), 28.4 (CH_2, C2), 26.3 (CH_2, C3). Anal. Calcd for $C_{10}H_{12}F_3NO_4$: C, 44.95; H, 4.53; N, 5.24. Found: C, 45.07; H, 4.61; N, 5.01. Data for **4c**: a white solid; mp 121.5–123.5 °C; IR (neat) ν_{max} 2945, 1757, 1682, 1626, 1281, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (br s, 1H, NH), 5.08 (d, *J*=1.5 Hz, 1H, H4′), 4.51 (dq, *J*=12.7, 8.4 Hz, 2H, C*H*$_2$CF$_3$), 4.39 (dq, *J*=12.7, 8.4 Hz, 2H, C*H*$_2$CF$_3$), 3.83 (s, 3H, OMe), 2.41 (dt, *J*=16.9, 7.8 Hz, 2H, H2), 2.27 (dt, *J*=16.6, 7.9 Hz, 2H, H2), 2.10 (t, *J*=7.8 Hz, 4H, H3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.9 (Cq, C5′), 173.2 (Cq, C3′), 171.3 (2C, Cq, C1), 122.0 (2C, q, $^1J_{C,F}$=275 Hz, Cq, *C*F$_3$), 95.0 (CH, C4′), 63.7 (Cq, C2′), 60.4 (2C, q, $^2J_{C,F}$=37 Hz, CH_2, O*C*H$_2$CF$_3$), 58.7 (CH_3, OMe), 30.8 (2C, CH_2, C2), 27.6 (2C, CH_2, C3). Anal. Calcd for $C_{15}H_{17}F_6NO_6$: C, 42.76; H, 4.07; N, 3.32. Found: C, 42.59; H, 3.95; N, 3.40.

4.3.2. 2,2,2-Trifluoroethyl 3-[(2R)-1-(4-methoxybenzyl)-2,5-dihydro-3-methoxy-5-oxo-1H-pyrrol-2-yl]propanoate (**3e**) and bis(2,2,2-trifluoroethyl) 3,3′-[1-(4-methoxybenzyl)-2,5-dihydro-3-methoxy-5-oxo-1H-pyrrole-2,2-diyl]dipropanoate (**4e**) (Table 1, entry 12)*

Prepared according to the representative VMMAR procedure and utilizing 1-(4-methoxybenzyl)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**1e**) (62 mg, 1.0 equiv) in place of **1c**. Reaction conditions: TMSOTf (48 μL, 1.0 equiv), Et_3N (37 μL, 1.0 equiv), reaction temperature −30 °C, reaction time 6 h. Purification via silica gel flash chromatography (hexane/EtOAc 30:70) afforded compound **3e** (19.5 mg, 19% yield), compound **4e** (33 mg, 23% yield), as well as recovered **1e** (35 mg, 57%). Data for **3e**: a pale yellow oil; IR (neat) ν_{max} 2941, 1756, 1682, 1627, 1512, 1246, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (br d, *J*=8.6 Hz, 2H, Ar), 6.83 (br d, *J*=8.6 Hz, 2H, Ar), 5.13 (s, 1H, H4′), 5.00 (1/2 ABq, *J*=15.1 Hz, 1H, C*H*$_2$Ar), 4.48 (dq, *J*=12.6, 8.4 Hz, 1H, C*H*$_2$CF$_3$), 4.40 (dq, *J*=12.6, 8.4 Hz, 1H, C*H*$_2$CF$_3$), 3.96 (1/2 ABq, *J*=15.1 Hz, 1H, C*H*$_2$Ar), 3.92 (t, *J*=3.8 Hz, 1H, H2′), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 2.20–2.30 (m, 2H, H2), 2.05–2.15 (m, 2H, H3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.8 (Cq, C5′), 171.7 (Cq, C1), 171.2 (Cq, C3′), 159.0 (Cq, Ar), 129.4 (Cq, Ar), 129.3 (2C, CH, Ar), 122.0 (q, $^1J_{C,F}$=275 Hz, Cq, *C*F$_3$), 114.1 (2C, CH, Ar), 94.6 (CH, C4′), 60.3 (q, $^2J_{C,F}$=37 Hz, CH_2, O*C*H$_2$CF$_3$), 58.2 (CH_3, OMe), 57.8 (CH, C2′), 55.2 (CH_3, OMe), 42.7 (CH_2, N*C*H$_2$Ar), 26.7 (CH_2, C2), 22.8 (CH_2, C3). Anal. Calcd for $C_{18}H_{20}F_3NO_5$: C, 55.81; H, 5.20; N, 3.62. Found: C, 55.69; H, 5.33; N, 3.50. Data for **4e**: a white solid; mp 87.2–88.9 °C; IR (neat) ν_{max} 2943, 1757, 1684, 1633, 1512, 1280, 1244, 1171 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (br d, *J*=8.6 Hz, 2H, Ar), 6.80 (br d, *J*=8.6 Hz, 2H, Ar), 5.31 (s, 1H, H4′), 4.20–4.50 (m, 6H, C*H*$_2$Ar and O*C*H$_2$CF$_3$), 3.78 (s, 3H, OMe), 3.77 (s, 3H, OMe), 1.80–2.10 (m, 8H, H2 and H3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.5 (Cq, C5′), 170.9 (Cq, C3′), 170.7 (2C, Cq, C1), 159.1 (Cq, Ar), 130.1 (Cq, Ar), 130.0 (2C, CH, Ar), 122.0 (2C, q, $^1J_{C,F}$=275 Hz, Cq, *C*F$_3$), 113.9 (2C, CH, Ar), 95.2 (CH, C4′), 67.3 (Cq, C2′), 60.2 (2C, q, $^2J_{C,F}$=36 Hz, CH_2, O*C*H$_2$CF$_3$), 58.4 (CH_3, OMe), 55.1 (CH_3, OMe), 41.4 (CH_2, N*C*H$_2$Ar), 29.0 (2C, CH_2, C2), 27.0 (2C, CH_2, C3). Anal. Calcd for $C_{23}H_{25}F_6NO_7$: C, 51.02; H, 4.65; N, 2.59. Found: C, 50.85; H, 4.83; N, 2.71.

4.3.3. (R)-4-Methoxy-5-[(R*)-2-nitro-1-phenylethyl]-1H-pyrrol-2(5H)-one (anti-**13**) and (R*)-4-methoxy-5-[(S*)-2-nitro-1-phenylethyl]-1H-pyrrol-2(5H)-one (syn-**13**) (Table 2, entry 1)*

Prepared according to the representative VMMAR procedure and utilizing 1-[(*E*)-2-nitrovinyl]benzene (**5**) in place of **2**. Reaction conditions: pyrrolinone **1c** (30 mg, 1.0 equiv), nitrostyrene **5** (79 mg, 2.0 equiv), TMSOTf (97 μL, 2.0 equiv), Et_3N (74 μL, 2.0 equiv), reaction temperature −78 °C, reaction time 8 h. ^{1}H NMR analysis of the crude reaction mixture revealed a >13:1 *anti*/*syn* diastereomeric ratio. The crude residue was purified by silica gel flash chromatography (DCM/MeOH 97.5:0.5) to afford compounds *anti*-**13** (48 mg, 69% yield) and *syn*-**13** (3 mg, 4% yield). Data for *anti*-**13**: a white solid; mp 62.0–64.0 °C; IR (neat) ν_{max} 2941, 1687, 1624, 1552, 1348, 1228 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2–7.4 (m, 5H, Ph), 6.46 (br s, 1H, NH), 5.08 (s, 1H, H3), 4.84 (dd, *J*=13.4, 9.1 Hz, 1H, H2′), 4.64 (dd, *J*=13.4, 5.7 Hz, 1H, H2′), 4.35 (br d, *J*=2.5 Hz, 1H, H5), 4.05 (ddd, *J*=9.0, 5.7, 3.0 Hz, 1H, H1′), 3.87 (s, 3H, OMe); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.1 (Cq, C2), 173.9 (Cq, C4), 135.9 (Cq, Ph), 129.2 (2C, CH, Ph), 128.4 (CH, Ph), 127.7 (2C, CH, Ph), 95.9 (CH, C3), 74.2 (CH_2, C2′), 60.2 (CH, C5), 58.7 (CH_3, OMe), 44.3 (CH, C1′). Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.66; H, 5.51; N, 10.55. Data for *syn*-**13**: colourless crystals; mp 183–185 °C; IR (neat) ν_{max} 2921, 1685, 1624, 1554, 1357, 1226 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 5H, Ph), 6.28 (br s, 1H, NH), 4.99 (dd, *J*=13.0, 8.0 Hz, 1H, H2′), 4.90 (s, 1H, H3), 4.78 (dd, *J*=13.0, 7.7 Hz, 1H, H2′), 4.38 (br d, *J*=5.8 Hz, 1H, H5), 3.85 (td, *J*=7.8, 5.9 Hz, 1H, H1′), 3.74 (s, 3H, OMe); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.9 (Cq, C2), 174.8 (Cq, C4), 133.7 (Cq, Ph), 128.7 (2C, CH, Ph), 128.5 (CH, Ph), 128.2 (2C, CH, Ph), 95.2 (CH, C3), 76.9 (CH_2, C2′), 58.5 (CH, C5), 58.4 (CH_3, OMe), 45.4 (CH, C1′). Anal. Calcd for $C_{23}H_{25}F_6NO_7$: C, 51.02; H, 4.65; N, 2.59. Found: C, 51.13; H, 4.71; N, 2.65. For crystal data, see infra. ORTEP plot, see Figure 1.

4.3.4. (R)-1-(4-Methoxybenzyl)-4-methoxy-5-[(R*)-2-nitro-1-phenylethyl]-1H-pyrrol-2(5H)-one (anti-**14**) and (R*)-1-(4-methoxybenzyl)-4-methoxy-5-[(S*)-2-nitro-1-phenylethyl]-1H-pyrrol-2(5H)-one (syn-**14**) (Table 2, entry 2)*

Prepared according to the representative VMMAR procedure and utilizing 1-[(*E*)-2-nitrovinyl]benzene (**5**) in place of **2** and pyrrolinone **1e** in place of **1c**. Reaction conditions: pyrrolinone **1e** (62 mg, 1.0 equiv), nitrostyrene **5** (79 mg, 2.0 equiv), TMSOTf (96 μL, 2.0 equiv), Et_3N (74 μL, 2.0 equiv), reaction temperature −78 °C, reaction time 2 h. ^{1}H NMR analysis of the crude reaction mixture revealed a 1.4:1 *anti*/*syn* diastereomeric ratio. Silica gel flash chromatographic purification (hexane/EtOAc 25:75) afforded 71 mg of an inseparable mixture of *anti*-**14** and *syn*-**14** in a 70% combined yield. Data for 1.4:1 *anti*-**14**/*syn*-**14** mixture: a glassy solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5×1.4H, Ph), 7.00–7.20 (m, 7H and 2×1.4H, Ar), 6.80–6.90 (m, 2H and 2×1.4H, Ar), 5.24 (1/2ABq, *J*=15.3 Hz, 1.4H, C*H*$_2$Ar), 5.16 (1/2ABq, *J*=15.1 Hz, 1H, C*H*$_2$Ar), 5.03 (s, 1.4H, H3), 4.96 (dd, *J*=13.9, 8.0 Hz, 1H, H2′), 4.93 (s, 1H, H3), 4.84 (dd, *J*=13.9, 7.1 Hz, 1H, H2′), 4.75–4.90 (m, 1.4H, H2′), 4.60–4.65 (m, 1.4H, H2′), 4.05–4.25 (m, 1H and 2×1.4H, H1′ and H5), 4.01 (br d, *J*=2.9 Hz, 1H, H5), 3.95 (1/2ABq, *J*=15.3 Hz, 1.4H, CH_2Ar), 3.91 (1/2ABq, *J*=15.0 Hz, 1H, CH_2Ar), 3.81 (s, 3×1.4H, OMe), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.70 (s, 3×1.4H, OMe); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.4 and 173.7 (Cq, C2), 172.3 and 171.6 (Cq, C4), 159.3 and 159.2 (Cq, Ar), 134.7 and 133.7 (Cq, Ar), 129.6 and 129.3 (3C, Cq, CH, Ar), 128.9 and 128.7 (2C, CH, Ar), 128.3 and 128.2 (CH, Ar), 128.1 and 127.8 (2C, CH, Ar), 114.3 and 114.2 (2C, CH, Ar), 96.0 and 95.3 (CH, C3), 75.0 and 74.9 (CH_2, C2′), 61.6 and 60.6 (CH, C5), 58.3 and 58.2 (CH_3, OMe), 55.3 and 55.2 (CH_3, OMe), 44.2 and 44.1 (CH, C1′), 43.2 and 42.5 (CH_2, N*C*H$_2$Ar).

4.3.5. Diethyl 2-{(R)-1-[(R*)-2,5-dihydro-3-methoxy-5-oxo-1H-pyrrol-2-yl]ethyl}malonate (anti-**15**) (Table 2, entry 4)*

Prepared according to the representative VMMAR procedure and utilizing diethyl 2-ethylidenemalonate (**6**) in place of **2**. Reaction conditions: pyrrolinone **1c** (30 mg, 1.0 equiv), malonate **6** (97 μL, 2.0 equiv), TMSOTf (97 μL, 2.0 equiv), Et_3N (74 μL, 2.0 equiv), reaction temperature −78 °C, reaction time 12 h. ^{1}H NMR analysis of the crude reaction mixture revealed a 30:1 *anti*/*syn* diastereomeric ratio. The crude residue was purified by silica gel flash chromatography (EtOAc) to afford compound *anti*-**15** in 98% yield. Data for *anti*-**15**: a pale yellow oil; IR (neat) ν_{max} 2981, 2941, 1731, 1685, 1622, 1460, 1367, 1269, 1230, 1174, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (br s, 1H, NH), 5.06 (d, *J*=0.8 Hz, 1H, H4″),

4.10–4.30 (m, 5H, OCH_2CH$_3$ and H2″), 3.81 (s, 3H, OMe), 3.58 (d, *J*=9.1 Hz, 1H, H2), 2.71 (dqd, *J*=9.1, 7.0, 3.2 Hz, 1H, H1′), 1.28 (br t, *J*=7.1 Hz, 6H, OCH$_2$CH_3), 0.98 (d, *J*=7.0 Hz, 3H, H2′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.7 (Cq, C5″), 173.8 (Cq, C3″), 168.3 and 168.2 (2Cq, *C*O$_2$Et), 95.2 (CH, C4″), 61.6 (2C, CH$_2$, OCH_2CH$_3$), 59.2 (CH, C2″), 58.4 (CH$_3$, OMe), 53.5 (CH, C2), 34.9 (CH, C1′), 14.0 (2C, OCH_2CH_3), 12.2 (CH$_3$, C2′). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.01; H, 7.18; N, 4.50. The presence of minor isomer *syn*-**15** evidenced by ^{1}H NMR analysis of the crude reaction product could no longer be detected after column chromatography purification. Data for *syn*-**15** (taken from the reaction mixture): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (br s, 1H, NH), 5.07 (br s, 1H, H4″), 4.10–4.30 (m, 5H, OCH_2CH$_3$ and H2″), 3.82 (s, 3H, OMe), 3.38 (d, *J*=8.2 Hz, 1H, H2), 2.70–2.85 (m, 1H, H1′), 1.25–1.35 (m, 6H, OCH$_2$CH_3), 0.83 (d, *J*=6.8 Hz, 3H, H2′).

4.3.6. *Diethyl 2-{(R*)-1-[(R*)-1-(4-methoxybenzyl)-2,5-dihydro-3-methoxy-5-oxo-1H-pyrrol-2-yl]ethyl}malonate (anti-**16**) and diethyl 2-{(S*)-1-[(R*)-1-(4-methoxybenzyl)-2,5-dihydro-3-methoxy-5-oxo-1H-pyrrol-2-yl]ethyl}malonate (syn-**16**) (Table 2, entry 5)*

Prepared according to the representative VMMAR procedure and utilizing diethyl 2-ethylidenemalonate (**6**) in place of **2** and pyrrolinone **1e** in place of **1c**. Reaction conditions: pyrrolinone **1e** (60 mg, 1.0 equiv), malonate **6** (94 μL, 2.0 equiv), TMSOTf (94 μL, 2.0 equiv), Et$_3$N (72 μL, 2.0 equiv), reaction temperature −78 °C, reaction time 12 h. ^{1}H NMR analysis of the crude reaction mixture revealed a 2:1 *anti*/*syn* diastereomeric ratio. Silica gel flash chromatographic purification (hexane/EtOAc 40:60) afforded *anti*-**16** as a colourless glassy solid (49.6 mg, 43% yield) and *syn*-**16** as a pale yellow glassy solid (24.2 mg, 21% yield). Data for *anti*-**16**: IR (neat) ν_{max} 2979, 2937, 1753, 1732, 1687, 1628, 1512, 1246 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J*=8.6 Hz, 2H, Ar), 6.84 (br d, *J*=8.7 Hz, 2H, Ar), 5.15 (s, 1H, H4″), 5.11 (1/2ABq, *J*=15.6 Hz, 1H, CH_2Ar), 4.00–4.20 (m, 4H, OCH_2CH$_3$), 3.90 (1/2ABq, *J*=15.3 Hz, 1H, CH_2Ar), 3.87 (br s, 1H, H2″), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.28 (d, *J*=9.9 Hz, 1H, H2), 2.94 (dqd, *J*=9.8, 7.3, 2.6 Hz, 1H, H1′), 1.27 (t, *J*=7.1 Hz, 3H, OCH$_2$CH_3), 1.23 (t, *J*=7.0 Hz, 3H, OCH$_2$CH_3), 0.98 (d, *J*=7.2 Hz, 3H, H2′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.1 (Cq, C5″), 172.3 (Cq, C3″), 168.0 (2C, Cq, *C*O$_2$Et), 158.9 (Cq, Ar), 129.3 (Cq, Ar), 129.1 (2C, CH, Ar), 114.1 (2C, CH, Ar), 95.1 (CH, C4″), 61.9 (CH, C2″), 61.6 and 61.5 (2C, CH$_2$, OCH_2CH$_3$), 58.2 (CH$_3$, OMe), 55.2 (CH$_3$, OMe), 53.5 (CH, C2), 43.2 (CH$_2$, NCH_2Ar), 33.0 (CH, C1′), 14.0 and 13.9 (2C, CH$_3$, OCH$_2$CH_3), 12.9 (CH$_3$, C2′). Anal. Calcd for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34. Found: C, 63.11; H, 7.08; N, 3.14. Data for *syn*-**16**: IR (neat) ν_{max} 2977, 2934, 1755, 1732, 1689, 1626, 1511, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J*=8.6 Hz, 2H, Ar), 6.84 (br d, *J*=8.7 Hz, 2H, Ar), 5.12 (s, 1H, H4″), 5.01 (1/2ABq, *J*=15.1 Hz, 1H, CH_2Ar), 4.00–4.20 (m, 4H, OCH_2CH$_3$), 4.02 (1/2ABq, *J*=15.1 Hz, 1H, CH_2Ar), 3.96 (d, *J*=2.4 Hz, 1H, H2″), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.70 (d, *J*=11.4 Hz, 1H, H2), 2.85 (dqd, *J*=11.0, 7.0, 2.4 Hz, 1H, H1′), 1.27 (t, *J*=7.1 Hz, 3H, OCH$_2$CH_3), 1.20 (t, *J*=7.0 Hz, 3H, OCH$_2$CH_3), 0.73 (d, *J*=6.9 Hz, 3H, H2′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.0 (Cq, C5″), 171.9 (Cq, C3″), 168.2 (Cq, *C*O$_2$Et), 168.0 (Cq, *C*O$_2$Et), 158.9 (Cq, Ar), 129.8 (Cq, Ar), 129.7 (2C, CH, Ar), 113.8 (2C, CH, Ar), 95.5 (CH, C4″), 61.6 and 61.5 (2C, CH$_2$, OCH_2CH$_3$), 60.3 (CH, C2″), 58.2 (CH$_3$, OMe), 55.2 (CH$_3$, OMe), 54.2 (CH, C2), 43.6 (CH$_2$, NCH_2Ar), 32.2 (CH, C1′), 14.0 and 13.9 (2C, CH$_3$, OCH$_2$CH_3), 10.2 (CH$_3$, C2′). Anal. Calcd for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34. Found: C, 62.82; H, 7.05; N, 3.50.

4.3.7. *(2E)-Diethyl 2-[3-methoxy-5-oxo-1H-pyrrol-2(5H)-ylidene]succinate (**17**) (Table 2, entry 6)*

Prepared according to the representative VMMAR procedure and utilizing diethyl but-2-ynedioate (**7**) in place of **2**. Reaction conditions: pyrrolinone **1c** (30 mg, 1.0 equiv), alkyne **7** (85 μL, 2.0 equiv), TMSOTf (97 μL, 2.0 equiv), Et$_3$N (74 μL, 2.0 equiv), reaction temperature −78 °C, reaction time 4 h. Silica gel flash chromatographic purification (hexane/EtOAc 33:67) afforded compound **17** (68.5 mg, 83% yield). Data for **17**: a white solid; mp 124–126 °C; IR (neat) ν_{max} 2983, 1738, 1697, 1602, 1333, 1274, 1176 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (br s, 1H, NH), 5.21 (d, *J*=1.5 Hz, 1H, H4′), 4.23 (q, *J*=7.1 Hz, 2H, OCH_2CH$_3$), 4.15 (q, *J*=7.1 Hz, 2H, OCH_2CH$_3$), 3.81 (s, 3H, OMe), 3.47 (s, 2H, H3), 1.30 (t, *J*=7.1 Hz, 3H, OCH$_2$CH_3), 1.24 (t, *J*=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.4 and 169.0 (2C, Cq, C3′ and C5′), 167.2 and 165.9 (2C, Cq, *C*O$_2$Et), 136.1 (C2′), 108.1 (C2), 95.1 (C4′), 61.4 (2C, CH$_2$, OCH_2CH$_3$), 58.5 (CH$_3$, OMe), 35.9 (CH$_2$, C3), 14.0 and 13.9 (2C, CH$_3$, OCH$_2$CH_3). Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.94. Found: C, 55.24; H, 5.94; N, 4.79.

4.3.8. *(2E)-Diethyl 2-[1-(4-methoxybenzyl)-3-methoxy-5-oxo-1H-pyrrol-2(5H)-ylidene]succinate (**18**) (Table 2, entry 7)*

Prepared according to the representative VMMAR procedure and utilizing diethyl but-2-ynedioate (**7**) in place of **2** and pyrrolinone **1e** in place of **1c**. Reaction conditions: pyrrolinone **1e** (62 mg, 1.0 equiv), alkyne **7** (85 μL, 2.0 equiv), TMSOTf (96 μL, 2.0 equiv), Et$_3$N (74 μL, 2.0 equiv), reaction temperature −70 °C, reaction time 4 h. Silica gel flash chromatographic purification (hexane/EtOAc 40:60) afforded compound **18** (42.4 mg, 37% yield), along with the expected VMMAR products (maleate isomer, 12%; fumarate isomer, 18%), as well as recovered pyrrolinone **1e** (13%). Data for **18**: IR (neat) ν_{max} 2981, 2937, 1731, 1707, 1612, 1514, 1336, 1246, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J*=8.8 Hz, 2H, Ar), 6.86 (br d, *J*=8.7 Hz, 2H, Ar), 5.32 (s, 1H, H4′), 4.92 (s, 2H, CH_2Ar), 4.23 (q, *J*=7.2 Hz, 2H, OCH_2CH$_3$), 4.16 (q, *J*=7.2 Hz, 2H, OCH_2CH$_3$), 3.85 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.32 (s, 2H, H3), 1.32 (t, *J*=7.2 Hz, 3H, OCH$_2$CH_3), 1.26 (t, *J*=7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.7 and 169.3 (2C, Cq, C3′ and C5′), 168.8 and 166.1 (2C, Cq, *C*O$_2$Et), 158.8 (Cq, Ar), 136.9 (C2′), 129.9 (Cq, Ar), 128.0 (2C, CH, Ar), 114.3 (2C, CH, Ar), 108.8 (C2), 93.2 (C4′), 61.5 and 61.4 (2C, CH$_2$, OCH_2CH$_3$), 58.6 (CH$_3$, OMe), 55.3 (CH$_3$, OMe), 43.9 (CH$_2$, NCH_2Ar), 35.9 (CH$_2$, C3), 14.1 and 14.0 (2C, CH$_3$, OCH$_2$CH_3). Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.39; H, 6.37; N, 3.40. Data for *diethyl 2-[(2R*)-1-(4-methoxybenzyl)-2,5-dihydro-3-methoxy-5-oxo-1H-pyrrol-2-yl]maleate* (not shown): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J*=8.5 Hz, 2H, Ar), 6.86 (br d, *J*=8.6 Hz, 2H, Ar), 5.97 (d, *J*=0.5 Hz, 1H, H3), 5.18 (1/2ABq, *J*=15.0 Hz, 1H, CH_2Ar), 5.11 (d, *J*=0.5 Hz, 1H, H4′), 4.41 (br s, 1H, H2′), 4.10–4.40 (m, 4H, OCH_2CH$_3$), 3.80 (s, 3H, OMe), 3.79 (1/2ABq, *J*=14.9 Hz, 1H, CH_2Ar), 3.78 (s, 3H, OMe), 1.25–1.35 (m, 6H, OCH$_2$CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.2 (Cq, C5″), 171.3 (Cq, C3″), 164.8 (Cq, *C*O$_2$Et), 163.8 (Cq, *C*O$_2$Et), 159.1 (Cq, Ar), 143.1 (Cq, C2), 129.7 (2C, CH, Ar), 129.0 (Cq, Ar),125.5 (CH, C3), 114.1 (2C, CH, Ar), 94.4 (CH, C4′), 62.0 and 61.8 (2C, CH$_2$, OCH_2CH$_3$), 61.4 (CH, C2′), 58.6 (CH$_3$, OMe), 55.3 (CH$_3$, OMe), 42.7 (CH$_2$, NCH_2Ar), 14.0 (2C, CH$_3$, OCH$_2$CH_3). Data for *diethyl 2-[(2R*)-1-(4-methoxybenzyl)-2,5-dihydro-3-methoxy-5-oxo-1H-pyrrol-2-yl]fumarate* (not shown): ^{1}H NMR (300 MHz, DMSO-d_6, 85 °C) δ 7.02 (d, *J*=8.6 Hz, 2H, Ar), 6.82 (d, *J*=8.6 Hz, 2H, Ar), 6.80 (s, 1H, H3), 5.70 (br s, 1H, H2′), 5.25 (s, 1H, H4′), 4.56 (1/2ABq, *J*=15.3 Hz, 1H, CH_2Ar), 4.10 (m, 4H, OCH_2CH$_3$), 3.97 (1/2ABq, *J*=15.3 Hz, 1H, CH_2Ar), 3.75 (s, 3H, OMe), 3.72 (s, 3H, OMe), 1.18 (m, 6H, OCH$_2$CH_3).

4.3.9. *(R*)-1-(4-Methoxybenzyl)-4-methoxy-5-[(R*)-3-oxocyclohexyl]-1H-pyrrol-2(5H)-one (anti-**19**) and (R*)-1-(4-methoxybenzyl)-4-methoxy-5-[(S*)-3-oxocyclohexyl]-1H-pyrrol-2(5H)-one (syn-**19**) (Table 2, entry 12)*

Prepared according to the representative VMMAR procedure and utilizing cyclohex-2-enone (**11**) in place of **2** and pyrrolinone **1e** in place of **1c**. Reaction conditions: pyrrolinone **1e** (60 mg, 1.0 equiv), ketone **11** (50 μL, 2.0 equiv), TMSOTf (94 μL, 2.0 equiv),

Et_3N (72 μL, 2.0 equiv), reaction temperature −20 °C, reaction time 12 h. ^1H NMR analysis of the crude reaction mixture revealed a 1.2:1 *anti*/*syn* diastereomeric ratio. Silica gel flash chromatographic purification (hexane/EtOAc 20:80) afforded *anti*-**19** and *syn*-**19** as a white solid in a 90% combined yield (75.3 mg). Data for 1.2:1 *anti*-**19**/*syn*-**19** mixture: ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J=8.5 Hz, 2×1.2H, Ar), 7.09 (d, J=8.4 Hz, 2H, Ar), 6.80–6.85 (m, 2×1.2H and 2H, Ar), 5.14 (s, 1.2H and 1H, H3), 5.12 (1/2ABq, J=15.2 Hz, 1H, CH_2Ar), 5.00 (1/2ABq, J=15.2 Hz, 1.2H, CH_2Ar), 4.04 (1/2ABq, J=15.2 Hz, 1.2H, CH_2Ar), 3.86 (1/2ABq, J=15.2 Hz, 1H, CH_2Ar), 3.79 (s, 6×1.2H and 6H, OMe), 3.75–3.80 (m, 1H, H5), 3.71 (d, J=2.1 Hz, 1.2H, H5), 2.45–2.55 (m, 1.2H, Alk), 2.35–2.40 (m, 1.2H and 1H, Alk), 2.1–2.3 (m, 3×1.2H and 3H), 1.9–2.1 (m, 1×1.2H and 2H), 1.3–1.9 (m, 3×1.2H and 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 183.2 and 182.8 (Cq, C3′), 175.1 and 174.7 (Cq, C2), 172.1 and 171.8 (Cq, C4), 159.0 (2C, Cq, Ar), 129.4 (2C, Cq, Ar), 129.2 and 129.1 (2C, CH, Ar), 114.1 and 114.0 (2C, CH, Ar), 95.3 and 94.9 (CH, C3), 62.6 and 62.2 (CH, C5), 58.2 (2C, OMe), 55.2 (2C, OMe), 43.5 and 43.0 (CH_2, NCH_2Ar), 43.4 and 41.8 (CH_2, Alk), 41.3 and 41.2 (CH_2, Alk), 38.5 and 38.3 (CH_2, Alk), 26.8 and 24.8 (CH_2, Alk), 25.4 and 25.2 (CH, Alk).

*4.3.10. 1-(4-Methoxybenzyl)-4-methoxy-5,5-bis(3-oxopentyl)-1H-pyrrol-2(5H)-one (**20**) (Table 2, entry 13)*

Prepared according to the representative VMMAR procedure and utilizing pent-1-en-3-one (**12**) in place of **2** and pyrrolinone **1e** in place of **1c**. Reaction conditions: pyrrolinone **1e** (60 mg, 1.0 equiv), ketone **12** (51 μL, 2.0 equiv), TMSOTf (94 μL, 2.0 equiv), Et_3N (72 μL, 2.0 equiv), reaction temperature 22 °C, reaction time 12 h. Silica gel flash chromatographic purification (hexane/EtOAc 40:60) afforded compound **20** (56 mg, 53% yield), along with a mono-alkylated γ-isomer (14 mg, 17%, not shown), as well as recovered **1e** (13 mg, 22%). Data for **20**: a white solid; IR (neat) ν_{max} 2937, 1712, 1676, 1630, 1512, 1342, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (br d, J=8.7 Hz, 2H, Ar), 6.78 (br d, J=8.6 Hz, 2H, Ar), 5.13 (s, 1H, H3), 4.29 (s, 2H, CH_2Ar), 3.75 (s, 3H, OMe), 3.74 (s, 3H, OMe), 2.0–2.2 and 1.8–2.0 (m, 12H, H1′, H2′, H4′), 0.93 (t, J=7.3 Hz, 6H, H5′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 209.7 (2C, Cq, C3′), 175.7 (Cq, C2), 171.3 (Cq, C4), 158.9 (Cq, Ar), 130.6 (Cq, Ar), 130.3 (2C, CH, Ar), 113.8 (2C, CH, Ar), 94.6 (CH, C3), 67.8 (Cq, C5), 58.2 (CH_3, OMe), 55.2 (CH_3, OMe), 41.3 (CH_2, NCH_2Ar), 35.7 (2C, CH_2, C2′ or C4′), 35.3 (2C, CH_2, C4′ or C2′), 28.2 (2C, CH_2, C1′), 7.6 (2C, CH_3, C5′). Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.65; H, 7.91; N, 3.40.

*4.3.11. X-ray structure determination of compound syn-**13***

Mp 183–185 °C; $C_{13}H_{14}N_2O_4$, M=262.29, T=298(2) K, λ=0.710373 Å, monoclinic, space group $P2_1/a$, a=9.406(1) Å, b=10.874(1) Å, c=13.126(2) Å, β=98.906(2)°, V=1326.4(3) $Å^3$, Z=4, d_{calcd}=1.313 Mg/m^3, μ=0.086 mm^{-1}, $F(000)$=552, crystal size=0.30×0.30×0.20 mm^3, reflections collected=14,733, independent reflections=2618 [R(int)=0.0305], refinement method=full-matrix least-squares on F^2, goodness-of-fit on F^2=1.075, final R indices [$I>2\sigma(I)$] R_1=0.0652, wR_2=0.2271, largest diff. peak and hole=0.70 and −0.31 e $Å^{-3}$.

Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 695318. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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14. For a comprehensive survey on these topics, see: Noteworthily, the presence of an alkoxy substituent at the C4 position of the ring influences the chemical

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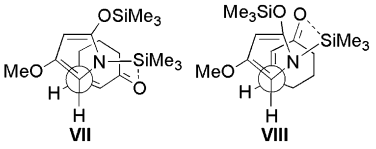
18. According to this line of reasoning, complete lack of reactivity between **1c** and *Z*-configured cyclic acceptor **11** could be attributed to the fact that both possible tight transition state models **VII** and **VIII** are sterically encumbered and inherently unfavoured.



VII **VIII**

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