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Organophosphorus Reagents in Organocatalysis: Synthesis of Optically Active α-Methylene-δ-lactones and δ-Lactams

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Abstract: In this paper we describe new asymmetric, catalytic strategies for the synthesis of biologically important α-methylene-δ-lactones and δ-lactams. The elaborated protocols utilize iminium-ion-mediated Michael addition of trimethyl phosphonoacetate to α,β-unsaturated aldehydes catalyzed by (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether as the key step. Enantiomerically enriched Michael adducts are employed in three different reaction pathways. Transformation into α-methylene-δ-lactones is realized by a sequence of reactions involving chemoselective reduction of the aldehyde, followed by a trifluoroacetic acid (TFA)-mediated cyclization and Horner–Wadsworth–Emmons olefination of formaldehyde. On the other hand, indolo[2,3-*a*]quinolizine-framework-containing products can be accessed when enantiomerically enriched Michael adducts are employed in a Pictet–Spengler reaction with tryptamine, followed by Horner–Wadsworth–Emmons olefination. Finally, reductive amination of the Michael adducts by using methylamine and Horner–Wadsworth–Emmons olefination of formaldehyde is demonstrated to give α-methylene-δ-lactams. The developed strategies can be realized without the purification of intermediates, thus greatly increasing their practicality.

Keywords: asymmetric catalysis · natural products · lactams · lactones · organophosphorus reagents

Introduction

The enantioselective synthesis of biologically active compounds is an important goal in modern organic and life-science chemistry. Identification of structural units responsible for molecular recognition constitutes an important part of the development of molecules for the life-science industry.[1] One example of such a motif is the α-alkylidene framework, which is present in many 5- and 6-membered lactones and lactams.[2] These compounds often exhibit strong cytotoxic activity, which is related to their ability to act as Michael acceptors in the reactions with various sulfur-bionucleophiles.[3] Importantly, many natural products containing these structural motifs have been isolated.[2,4] Selected examples of natural α-alkylidene-δ-lactones and δ-lactams are shown in Figure 1. For instance, α-methylene-δ-lactones can be found in vernolepin, which was isolated from *Vernonia hymenolepis* in the 1960s.[4a] Other natural products containing δ-lactones ring such as: teucriumlactone[4b] and pentalenolactone E[4c] are also known. Contrarily, α-alkylidene-δ-lactams are less common in nature. Gelegamine B, recently isolated from *Gelsemiumelegan*, constitutes one such example.[4d] Nonetheless, these compounds have found interesting synthetic applications. For example, α-methylene-δ-lactams **A** and **B** were used as key intermediates in the synthesis of codeine analogues.[5] Moreover, α-alkylidene-δ-lactam **C** is a synthetic precursor of geissoschizine, a natural indolo[2,3-*a*]quinolizine alkaloid.[6] This class of natural products has recently received considerable attention.[7]

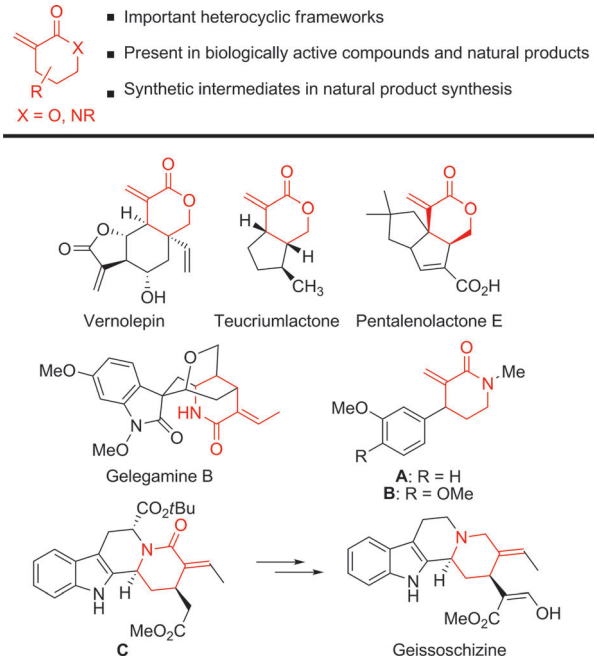

Figure 1. The importance of α-alkylidene-δ-lactones and δ-lactams.

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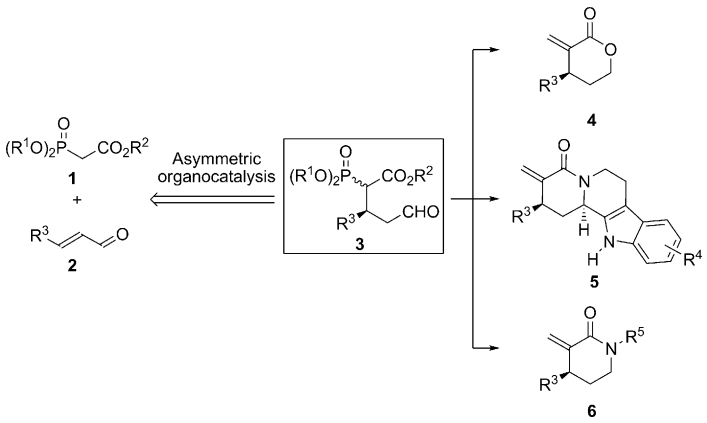
In the past 10 years, the synthesis of small molecules containing α-alkylidene lactones and lactams structural units as potential drug precursors has received considerable attention.[8] These heterocyclic moieties constitute an interesting template for the drug discovery process. However, since biological activity of chiral compounds is very often related to absolute configuration of their stereogenic centers, an enantioselective synthesis of structural motifs that exhibit strong biological activity constitutes an important challenge for chemical society. Surprisingly, enantioselective methods leading to these α-alkylidene-δ-lactones and δ-lactams are scarcer.[2f,9]

Given the importance of α-alkylidene-δ-lactones **4** and δ-lactams **5** and **6** structural units, studies on the development of asymmetric organocatalytic strategies[10] for their synthesis were undertaken (Scheme 1). At the outset of the studies, the diversity of the methodology was one of the main goals. It was envisioned that the 3-substituted-2-(dialkoxyphosphoryl)-5-oxoalkanoates **3** can serve as common precursors of various products containing the α-methylene-δ-lactone **4** and δ-lactam **5** and **6** motifs. Importantly, the alkanoate intermediates **3** should be readily available through iminium-ion-mediated Michael addition of trialkyl phosphonoacetate **1** to α,β-unsaturated aldehydes **2** catalyzed by chiral secondary amine. It was devised that the enantiomerically enriched 3-substituted-2-(dialkoxyphosphoryl)-5-oxoalkanoates **3** obtained can be utilized in three different reaction strategies leading to α-methylene-δ-lactones **4**, as well as α-methylene-δ-lactams **5** and **6**. It was anticipated that a sequence of reactions initiated by chemoselective reduction of the aldehyde, followed by lactonization and Horner–Wadsworth–Emmons (HWE) reaction with formaldehyde should afford α-methylene-δ-lactones **4**. Furthermore, α-methylene-δ-lactams **5** possessing indolo[2,3-*a*]quinolizine alkaloid framework could be obtained by means of Pictet–Spengler reaction[11] of alkanoates **3** with tryptamines followed by HWE reaction with formaldehyde. Importantly, the second group of α-methylene-δ-lactams **6** should be accessible through reductive amination of **3** and HWE olefination of formaldehyde further diversifying the scope of the methodology. However, the main challenges related to the preservation of optical activity introduced in the first organocatalytic step and throughout the reaction sequences were of major concern. Furthermore, in terms of practicality of the methodology main focus was given to the development of methods allowing for access to target products without isolation or at least purification of the intermediates. It is also worth noting that the present work constitutes the first example of enantioselective synthesis of β-substituted-α-methylene-δ-lactones **4** and δ-lactams **5** and **6**.

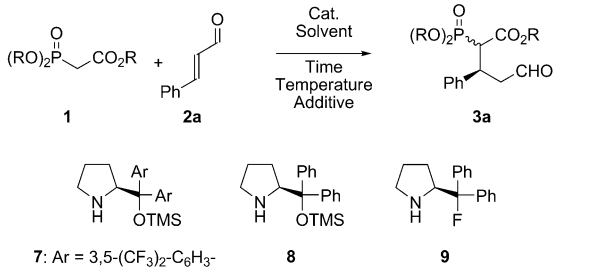


Scheme 1. Asymmetric organocatalytic strategy for the synthesis of α-methylene-δ-lactones **4** and lactams **5** and **6**.

Results and Discussion

The optimization studies were initiated with a goal of finding the optimal reaction conditions for the Michael addition of trialkyl phosphonoacetates **1** to α,β-unsaturated aldehydes **2**. Triethyl phosphonoacetate **1a** and cinnamaldehyde **2a** were chosen as model substrates (Table 1). At the outset of the studies different catalysts and solvents were evaluated. Initial experiments performed under conditions described for the Michael addition of malonates to α,β-unsatu-

Table 1. Addition of trialkyl phosphonoacetate **1** to cinnamaldehyde **2a**: Screening results.[a]

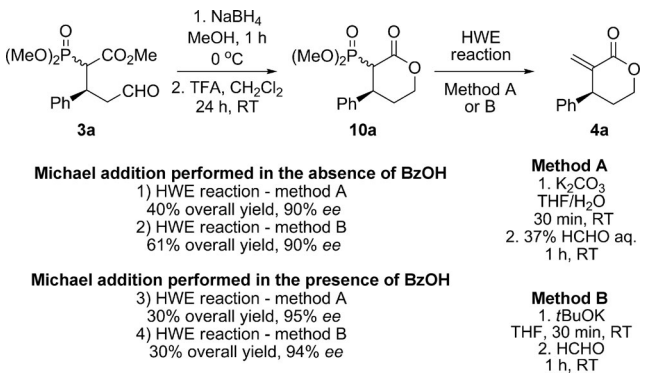


Entry	R	Catalyst (loading) [mol%]	*T* [°C]	*t* [h]	Solvent	Additive[b]	Conv. [%][c]	*ee* [%][d]
1	Et	**7** (10)	RT	24	EtOH	–	0	nd
2	Et	**8** (10)	RT	24	EtOH	–	50	nd
3	Et	**8** (10)	RT	48	EtOH	–	50	nd
4	Et	**9** (10)	RT	72	EtOH	–	55	nd
5	Et	**9** (10)	RT	168	EtOH	–	78	nd
6	Et	**9** (20)	RT	24	CH_2Cl_2	–	0	nd
7	Et	**9** (20)	RT	72	MeOH	–	86	nd
8	Me	**8** (20)	RT	24	MeOH	–	92	90
9	Me	**8** (20)	RT	24	MeOH	BzOH	83	95
10	Me	**8** (20)	0	24	MeOH	BzOH	83	nd
11	Me	**8** (20)	40	24	MeOH	–	82	70
12	Me	**8** (10)	RT	24	MeOH	–	60	nd
13	Me	**9** (20)	RT	24	MeOH	–	88	80
14	Me	**9** (20)	RT	72	MeOH	BzOH	80	80
15	Me	**9** (20)	40	24	MeOH	BzOH	76	70
16	Me	**8** (20)	40	48	MeOH	BzOH	75	80

[a] All reactions were performed at 0.2 mmol scale in appropriate solvent (0.4 mL). [b] 10 mol% applied. [c] Estimated by ^{31}P NMR spectroscopic analysis of the crude reaction mixture. [d] Determined by HPLC on a chiral stationary phase after transformation into the corresponding α-methylene-δ-lactone **4a**.

rated aldehydes **2**[12] showed that 2-[bis(3,5-bis(trifluoromethyl)phenyl)(trimethylsilyloxy)methyl]pyrrolidine **7** does not catalyze the reaction (Table 1, entry 1). On the contrary, α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **8** and 2-(fluorodiphenylmethyl)pyrrolidine **9** proved successful (Table 1, entries 2–5) but the conversion was unsatisfactory. Further screening revealed that the reaction outcome strongly depends on the solvent used. For instance, in chlorinated solvent such as CH_2Cl_2 the reaction was suppressed (Table 1, entry 6). Gratifyingly, the best conversion was obtained in MeOH (Table 1, entry 7); however, the formation of transesterification products was observed. For this reason, trimethyl phosphonoacetate **1b** was used instead of triethyl phosphonoacetate **1a** as a nucleophilic reagent in the further studies. To our delight, the reaction in MeOH was faster and was terminated within 24 h and for both catalyst **8** and **9** good results (92 and 88% conversion, respectively) were obtained (Table 1, entries 8 and 13). In the course of further studies, the influence of acidic additive as well as reaction temperature and amount of the catalyst on the reaction outcome were evaluated. When benzoic acid was employed as acidic co-catalyst, no improvement in the conversion was observed (Table 1, entries 9, 10 and 14–16). The change of temperature did not increase the conversion (Table 1, entries 10, 11, 15, and 16). In terms of catalyst loading, employment of 10 mol% of the catalyst suppressed the reaction rate significantly (Table 1, entry 12). It should be also noted that at this stage the determination of enantioselectivity of the Michael addition step was impossible due to Michael adducts being very prone to retro-Michael reaction. Therefore, transformation of a model methyl 2-(dimethoxyphosphoryl)-5-oxo-3-phenylpentanoate **3a** into the target α-methylene-δ-lactone **4a** was performed in a sequence of reactions involving chemoselective reduction of the aldehyde by $NaBH_4$ followed by a trifluoroacetic acid (TFA)-mediated cyclization and HWE olefination with formaldehyde (for detailed optimization studies of the reaction sequence, see below). Enantiomeric excess determination revealed that in terms of catalyst used, α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **8** gave better enantioselectivity than 2-(fluorodiphenylmethyl)pyrrolidine **9** catalyst (Table 1, entries 8, 9, 14, and 15). Furthermore, the use of acidic additive led to increase of enantioselectivity (Table 1, entry 9). The elevated temperature of the Michael addition step led to diminished enantioselectivity (Table 1, entries 11, 15, and 16). In general, the best results were obtained using α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **8** in the presence of benzoic acid or without the acid (Table 1, entries 8 and 9).

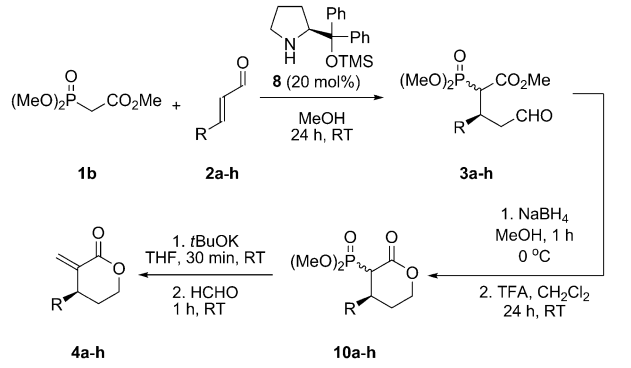
Parallel to the optimization studies of the enantioselective Michael addition of trimethyl phosphonoacetate **1b** to cinnamaldehyde **2a**, the transformation of methyl 2-(dimethoxyphosphoryl)-5-oxo-3-phenylpentanoate **3a** into the target α-methylene-δ-lactone **4a** was attempted (Scheme 2). Chemoselective reduction of the aldehyde in **3a** was performed using $NaBH_4$ in MeOH at 0°C affording δ-hydroxypentanoate, which cyclized in the presence of TFA to α-dimethoxyphosphoryl-δ-lactone **10a**. This product was formed as a mixture of two diastereoisomers in a ratio of 95:5. However, since the main focus of the work was on the development of a reaction sequence leading to the target α-methylene-δ-lactones **4** without purification of any intermediates, crude α-dimethoxyphosphoryl-δ-lactone **10a** was utilized in the HWE olefination applying formaldehyde. It was found that the overall yield of the reaction sequence (consisting of four subsequent reactions) was dependent on two main factors: Firstly, the conditions applied in the HWE olefination step. Secondly, the presence of acidic co-catalyst in the Michael addition step. The use of potassium *tert*-butoxide as a base and solid paraformaldehyde proved superior to potassium carbonate/formaline combination when the Michael adduct **3a** obtained in the absence of acidic co-catalyst was utilized. On the contrary, both HWE reaction conditions performed similarly when Michael adduct **3a** obtained in the presence of acidic co-catalyst was applied. Furthermore, the presence of acidic additive in the Michael addition step led to lower overall yields when compared with the reactions performed in its absence. Delightfully, the presence of acid had a beneficial influence on the stereochemical outcome of the reaction sequence, resulting in higher enantioselectivities. These interesting observations suggest that the Michael addition step is more reversible in the presence of acidic co-catalyst leading to overall yield deterioration.



Scheme 2. Transformation of enantiomerically enriched Michael adduct **3a** into optically active α-methylene-δ-lactone **4a**.

With the optimized conditions for the enantioselective formation of α-methylene-δ-lactones **4** in hand, we turned our attention to the scope of the methodology (Table 2). To our delight, various aromatic α,β-unsaturated aldehydes **2a–h** could participate in the reaction sequence leading to the formation of the desired α-methylene-δ-lactones **4a–h**. Reaction of the cinnamaldehydes **2e–h** bearing electron-donating groups on the aromatic ring (Table 2, entries 8–12) proceeded with slightly lower yields and enantioselectivities compared with the aromatic enals bearing electron-withdrawing groups **2b–d** (Table 2, entries 3–7). Importantly, good enantiomeric excesses and yields were obtained independent on the substitution pattern of the aromatic ring. Notably, α-methylene-δ-lactones **4f–h** bearing alkyl groups on the aromatic ring were obtained with slightly reduced

Table 2. Enantioselective Synthesis of α-Methylene-δ-lactones **4a–h**.[a]



Entry	R	Additive	Yield [%][b]	*ee* [%][c]
1	Ph (**2a**)	–	61	**4a** (90)
2	Ph (**2a**)	BzOH	30	**4a** (94)
3	4-$NO_2C_6H_4$- (**2b**)	–	80	**4b** (92)
4	4-$NO_2C_6H_4$- (**2b**)	BzOH	32	**4b** (94)
5	2-BrC_6H_4- (**2c**)	–	70	**4c** (91)
6	2-BrC_6H_4- (**2c**)	BzOH	38	**4c** (95)
7	4-ClC_6H_4- (**2d**)	–	58	**4d** (93)
8	2-$CH_3OC_6H_4$- (**2e**)	–	62	**4e** (90)
9	2-$CH_3OC_6H_4$- (**2e**)	BzOH	28	**4e** (94)
10[d]	4-$CH_3C_6H_4$- (**2f**)	–	48	**4f** (86)
11[d]	4-*t*BuC_6H_4- (**2g**)	–	65	**4g** (84)
12[d]	3,5-$(CH_3)_2C_6H_4$- (**2h**)	–	52	**4h** (88)

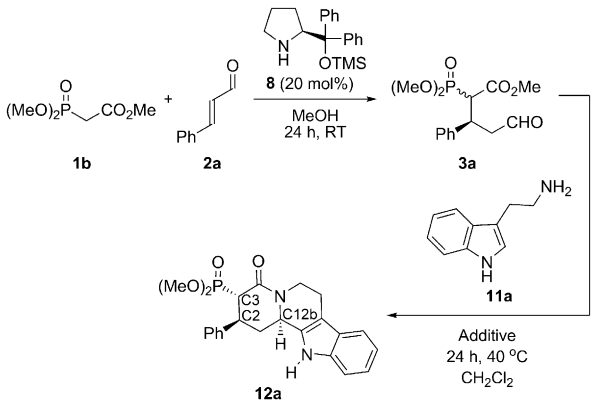
[a] Michael additions performed at 0.2 mmol scale with 20 mol% of the catalyst (*S*)-**8** in MeOH (0.4 mL) for 24 h at RT. [b] Overall yield for 4 steps. [c] Determined by HPLC on a chiral stationary phase after transformation into the corresponding α-methylene-δ-lactones **4a–h**. [d] Michael addition performed for 48 h.

yield and enantioselectivity (Table 2, entries 10–12). Interestingly, the same influence of the acidic additive on the overall reaction sequence outcome—significantly lower yields and slightly better enantioselectivities—was observed (Table 2, entries 2, 4, 6, and 9). Disappointingly, when aliphatic aldehydes were applied in the Michael addition step under optimized reaction conditions the desired product was not obtained.

Having accomplished the enantioselective synthesis of β-substituted-α-methylene-δ-lactones **4a–h**, the reaction sequences leading to optically active α-methylene-δ-lactams **5** and **6** were investigated (Scheme 1). We became particularly interested in the development of reaction sequence leading to the formation of α-methylene-δ-lactams **5** having the core of corynantheoid alkaloids incorporated. Such products should be accessed when enantiomerically enriched Michael adducts are employed in Pictet–Spengler reaction with tryptamine followed by HWE olefination. It is worth noting that in the Pictet–Spengler reaction a new stereogenic center is formed and diastereoselectivity of the reaction is an important issue. In the first attempt, enantiomerically enriched Michael adduct **3a** and tryptamine **11a** were heated in CH_2Cl_2 at 40 °C; however, only the retro-Michael reaction was observed (Table 3, entry 1). Delightfully, when the reaction was performed in the presence of benzoic acid as acidic additive, the formation of desired product occurred (Table 3, entry 2). In the course of the further studies, other Brønsted acids such as 2-fluorobenzoic acid, metanosulfonic acid, TFA, and 3,5-bis(trifluoromethyl)benzoic acid were evaluated in the reaction (Table 3, entries 3–7). It was observed that the strength of the acidic additive had significant influence on the reaction outcome. The best results were obtained using 3,5-ditrifluoromethylbenzoic acid (Table 3, entry 5) providing the target α-dimethoxyphosphoryl-δ-lactam **12a** in 74% yield and with good diasteroselectivity (diasteromeric ratio (d.r.) = 90:10). However, at this stage we were unable to determine if the obtained diastereoisomers differed at the C3 or C12b stereogenic center. Notably, the use of TFA as acidic additive led to an improvement in diastereoselectivity, but with a slightly reduction of the yield to 67% (Table 3, entry 6). Interestingly, the use of very strong acid such as methanesulfonic acid led to the formation of complex reaction mixture (Table 3, entry 7).

It should be noted that in the case of this reaction sequence, the corresponding α-dimethoxyphosphoryl-δ-lactams **12** had to be isolated by flash chromatography. Initial studies showed that when crude reaction mixtures were utilized directly in the HWE reaction *N*-alkylation was occurring as well. For this reason the nitrogen atom of the indole ring was Boc-protected. It was found that efficiency of this reaction highly depends on the purity of starting lactam **12a**

Table 3. Optimization of the reaction conditions for the synthesis of the α-dimethoxyphosphoryl-δ-lactam **12a**.[a]



Entry	Additive	Conv. [%]	Yield [%]	d.r.[b] [%]
1	–	retro-Michael reaction	nd	nd
2	BzOH	75	64	90:10
3	2-FC_6H_4COOH	66	56	90:10
4	3,5-$(NO_2)_2C_6H_3CO_2H$	76	nd	90:10
5	3,5-$(CF_3)_2C_6H_3CO_2H$	85	74	90:10
6	TFA	85	67	95:5
7	CH_3SO_3H	decomposition	nd	nd

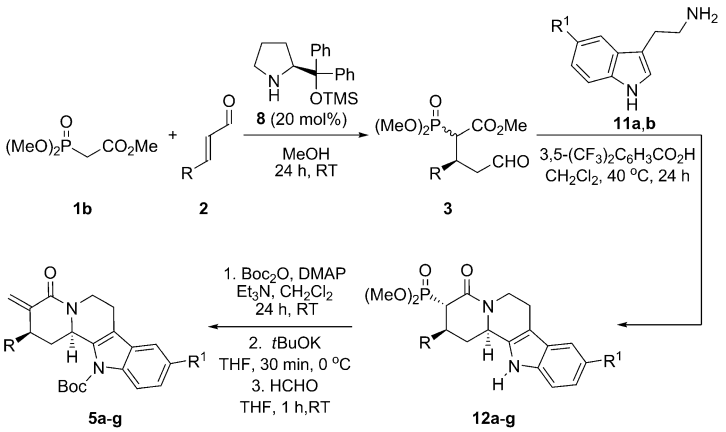
[a] Michael additions performed at 0.2 mmol scale with 20 mol% of the catalyst (*S*)-**8** in MeOH (0.4 mL) for 24 h at RT. [b] Estimated by ^{31}P NMR spectroscopic analysis of the crude reaction mixture.

indicating the necessity of purification of **12** by means of flash chromatography. To our delight, a subsequent reaction sequence involving Boc-protection and HWE olefination of formaldehyde could be performed without purification of the intermediate affording target product **5a** in good yield. Notably, lactam **5a** was formed as single diastereoisomer. This result indicates that diastereoisomeric α-dimethoxyphosphoryl-δ-lactams **12a** differ in configuration at the C3 stereogenic center and Pictet–Spengler reaction is fully diastereoselective. Furthermore, enantioselectivity introduced in the Michael addition was preserved throughout the sequence as the final product was obtained with an enantiomeric excess (*ee*) of 92%.

With optimized conditions for the reaction sequence leading to the formation of indolo[2,3-*a*]quinolizines-framework-containing products **5** in hand, the scope of the methodology was studied (Table 4). Gratifyingly, α-dimethoxyphosphoryl-δ-lactams **12a–g** derived from both electron-poor (Table 4, entries 2–4) and electron-rich (Table 4, entries 5 and 6) enals **2** could be obtained in good yields (58–80%) and good diasteroselectivities (90:10 to 95:5 d.r.) employing the optimized reaction conditions. Importantly, substituted tryptamines can be utilized in the developed reaction sequence as demonstrated for 5-methoxy derivative **11b** leading to the formation of lactam **12g** in 88% yield and with 90:10 d.r. (Table 4, entry 7). Subsequent, two step protocol enabled efficient introduction of α-methylene moiety yielding target products **5b–g** in good yields and as single diastereoisomers. Importantly, high enantioselectivities (86–94% *ee*) were obtained indicating high compatibility of the organocatalytic step with subsequent transformations.

Being successful in establishing an efficient enantioselective methodology for the synthesis of indolo-[2,3−*a*]quinolizines-framework-containing products **5a–g**, the development of second synthetic pathway to α-methylene-δ-lactams **6** was investigated (Table 5). For this reason, enantiomerically enriched 5-oxopentanoates **3** were subjected to reductive amination using methylamine as aminating reagent and sodium borohydride as reducing agent.[8e] Under these reaction conditions, the δ-aminopentanoates underwent spontaneous lactamizations yielding α-dimethoxyphosphoryl-δ-lactams **13** as single diastereoisomers. Subsequently, HWE olefination of paraformaldehyde in the presence of potassium *tert*-butoxide as a base in THF was performed. The developed procedure involves only one isolation protocol–an extraction performed after reductive amination step. Various electron-poor and electron-rich α,β-unsaturated aldehydes **2** were tested in this reaction sequence (Table 5, entries 1–5). It is worth noting that the reactions of the aldehydes with electron-donating groups on the aromatic ring, **2e** and **2h** (Table 5, entries 4 and 5), proceeded with lower yield (26–27%) and enantioselectivities (88 and 82% *ee*) when compared with enals substituted with electron-withdrawing substituents **2b** and **2d** (48–49% yield, 90–94% *ee*; Table 5, entries 2 and 3).

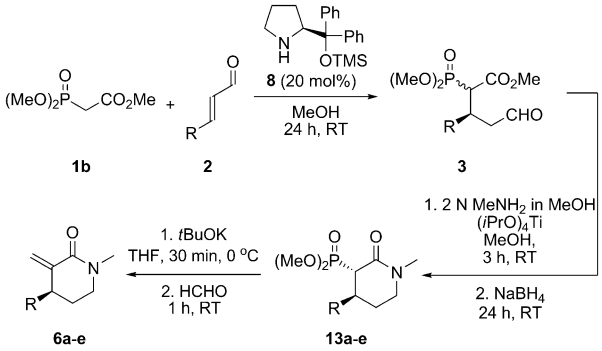
Table 4. Scope of the enantioselective synthesis of optically active α-methylene-δ-lactams **5a–g**.[a]



Entry	R	R^1	d.r.[b] **12**	Yield [%] **12**[c]	Yield [%] **5**[c]	*ee* [%][d]
1	Ph (**2a**)	H (**11a**)	90:10	80	55	**5a** (92)
2[e]	4-$NO_2C_6H_4$- (**2b**)	H (**11a**)	95:5	80	69	**5b** (94)
3	4-ClC_6H_4- (**2d**)	H (**11a**)	90:10	70	45	**5c** (87)
4[e]	4-$CF_3C_6H_4$- (**2i**)	H (**11a**)	95:5	58	72	**5d** (94)
5	2-$CH_3OC_6H_4$- (**2e**)	H (**11a**)	90:10	61	50	**5e** (90)
6[e]	3,5-$(CH_3)_2C_6H_3$- (**2h**)	H (**11a**)	90:10	62	53	**5f** (86)
7	Ph (**2a**)	OMe (**11b**)	90:10	88	63	**5g** (92)

[a] Michael additions performed at 0.2 mmol scale with 20 mol% of the catalyst (*S*)-**8** in MeOH (0.4 mL) for 24 h at RT. [b] Estimated by ^{31}P NMR spectrocopic analysis of the crude reaction mixture. [c] Overall yield for 2 steps. [d] Determined by HPLC on a chiral stationary phase after transformation into the corresponding α-methylene-δ-lactams **5a–g**. [e] Michael addition performed for 48 h.

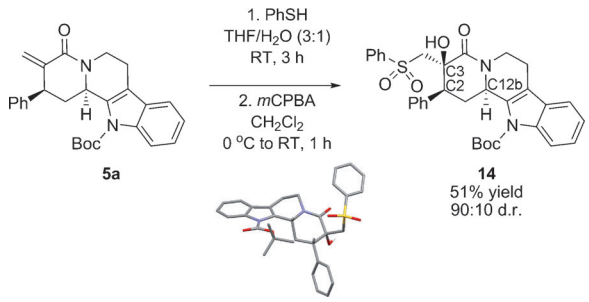
Table 5. Enantioselective synthesis of α-methylene-δ-lactams **6a–e**.[a]



Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph (**2a**)	50	**6a** (92)
2[d]	4-$NO_2C_6H_4$- (**2b**)	49	**6b** (94)
3[d]	4-ClC_6H_4- (**2d**)	48	**6c** (90)
4	2-$CH_3OC_6H_4$- (**2e**)	26	**6d** (88)
5[d]	3,5-$(CH_3)_2C_6H_3$- (**2h**)	27	**6e** (82)

[a] Michael additions performed at 0.2 mmol scale with 20 mol% of the catalyst (*S*)-**8** in MeOH (0.4 mL) for 24 h at RT. [b] Overall yield for 4 steps. [c] Determined by HPLC on a chiral stationary phase after transformation into the corresponding α-methylene-δ-lactams **6a–e**. [d] Michael addition performed for 48 h.

All of the products obtained have an electron-deficient alkene moiety, which is well-suited for the application in the Michael addition. For this reason and inspired by the ability of these compounds to react with sulfur-biomolecules,[3] the thio-Michael addition of thiophenol to α-methylene-δ-lactam **5a** was performed yielding the corresponding adduct as a single diastereoisomer.[13] This product was directly subjected to *meta*-chloroperbenzoic acid (*m*CPBA) oxidation yielding sulfone **14** (Scheme 3). Interestingly, under reaction



Scheme 3. Synthesis and X-ray structure of **14**.[a]

conditions concomitant α-oxidation occurred enabling introduction of the quaternary stereogenic center in 90:10 d.r.[14] Importantly, this transformation allowed us to assign absolute configuration of the lactams **5**. Single-crystal X-ray analysis of **14**[15] indicated *cis*-configuration of H2 and H12b protons (Scheme 3). This result shows that the acid-mediated Pictet–Spengler reaction leads to the formation of the "thermodynamic" stereochemistry of quinolizidine alkaloid core.[7d,f] Furthermore, the absolute configuration of the stereogenic center originating from iminium ion-mediated Michael addition turned out to be in accordance with related Michael reactions catalyzed by (*S*)-**8**[10l,12]-trimethyl phosphonoacetate, which approaches the iminium-activated enal from the site opposite to the bulk of the catalyst. Importantly, since all target α-methylene-δ-lactones **4** and lactams **5** and **6** obtained are derived from the same common precursors **3**, the absolute configuration of **4**, **5**, and **6** was assigned by analogy.

Conclusion

We have developed new asymmetric organocatalytic protocols for the synthesis of α-methylene-δ-lactones and δ-lactams with very good enantioselectivites and yields starting from easily available substrates. Developed strategies utilize Michael addition of trimethyl phosphonoacetate to aromatic enals as a key enantiodifferentiating step using α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether as a catalyst. Subsequent transformations leading to target compounds can be realized without purification of intermediates, greatly increasing their practicality. Importantly, enantiomeric enrichment introduced in the first, organocatalytic step can be preserved throughout the reaction sequences and final α-methylene-δ-lactones and δ-lactams can be accessed in a highly stereoselective fashion.

Experimental Section

General procedure for the preparation of α-methylene-δ-lactones 4a–h: In an ordinary vial, the corresponding aldehyde (0.4 mmol) was added to a solution of catalyst (13 mg, 0.04 mmol) in MeOH (0.4 mL). After 15 min, trimethyl phosphonoacetate (36 mg, 0.2 mmol) was added and the resulting mixture was stirred overnight at room temperature. After complete consumption of trimethyl phosphonoacetate (monitored by ^{31}P NMR spectroscopy), MeOH (1 mL) was added to the vial, which was then cooled to 0 °C and $NaBH_4$ (38 mg, 1 mmol) was added in portions. The resulting mixture was left at 0 °C for 1 h, quenched with 2 N HCl (5 mL), and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 mL), TFA (0.5 mL) was added and the resulting solution was left at room temperature overnight. Then CH_2Cl_2 (10 mL) was added and washed with saturated $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Resulting crude α-dimethoxyphosphoryl-δ-lactone (1.0 equiv) was dissolved in THF (to obtain 1 M solution) and potassium *tert*-butoxide (1.2 equiv) was added at room temperature. The resulting mixture was stirred at room temperature for 30 min. Then paraformaldehyde (5.0 equiv) was added at room temperature and the stirring was continued for 1 h. The mixture was then quenched with sat. NaCl solution (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by FC on silica gel to afford the target α-methylene-δ-lactone **4**.

General procedure for the preparation of α-dimethoxyphosphoryl-δ-lactams 12a–g: In an ordinary vial, the corresponding aldehyde (0.4 mmol) was added to a solution of catalyst (13 mg, 0.04 mmol) in MeOH (0.4 mL). After 15 min trimethyl phosphonoacetate (36 mg, 0.2 mmol) was added and the resulting mixture was stirred overnight at room temperature. After complete consumption of trimethyl phosphonoacetate (monitored by ^{31}P NMR spectroscopy), MeOH was evaporated and the crude Michael adduct **3** was dissolved in CH_2Cl_2 (1 mL), then tryptamine (0.22 mmol, 35 mg) and 3,5-bis(trifluoromethyl)benzoic acid (0.3 mmol, 77 mg) were added. The reaction was stirred for 24 h at reflux. Then aq. sat. $NaHCO_3$ (10 mL) was added, and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over $MgSO_4$. The crude product was purified by FC to afford target α-dimethoxyphosphoryl-δ-lactam **12**.

General procedure for the preparation of α-methylene-δ-lactams 5a–g: Lactam **12** (0.12 mmol) was dissolved in CH_2Cl_2 (2 mL) and triethylamine was added (42 μL, 0.3 mmol). After stirring for 10 min at room temperature, $(Boc)_2O$ (40 mg, 0.18 mmol) and DMAP (3.7 mg, 0.03 mmol) were added and the reaction mixture was stirred for 24 h at room temperature. Then the reaction was diluted with CH_2Cl_2 (10 mL) and washed with aq. sat. NH_4Cl (5 mL), aq. sat. $NaHCO_3$ (5 mL), and brine (5 mL). The crude *N*-protected-α-dimethoxyphosphoryl-δ-lactam (1.0 equiv) was dissolved in THF (to obtain 1 M solution) potassium *tert*-butoxide (1.2 equiv) was added at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. Then paraformaldehyde (5.0 equiv) was added at room temperature and the stirring was continued for 1 h. The mixture was then quenched with sat. NaCl solution (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by FC on silica gel to afford target α-methylene-δ-lactam **5**.

General procedure for the preparation of α-methylene-δ-lactams 6a–e: In an ordinary vial, the corresponding aldehyde (0.4 mmol) was added to a solution of catalyst (13 mg, 0.04 mmol) in MeOH (0.4 mL). After 15 min, trimethyl phosphonoacetate (36 mg, 0.2 mmol) was added and the resulting mixture was stirred overnight at room temperature. After complete consumption of trimethyl phosphonoacetate (monitored by ^{31}P NMR spectroscopy) solution of $Ti(OiPr)_4$ (74 mg, 0.26 mmol), 2 N solution of $MeNH_2$ in MeOH (130 μL, 0.26 mmol) were added at room

temperature. The reaction mixture was stirred for 3 h, then $NaBH_4$ (8 mg, 0.2 mmol) was added in one portion. Stirring was continued for 24 h. The water (15 mL) was added and MeOH was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (4×20 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a crude α-dimethoxyphosphoryl-δ-lactam (1.0 equiv), which was dissolved in THF (to obtain 1 M solution) and potassium *tert*-butoxide (1.2 equiv) was added at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. Then, paraformaldehyde (5.0 equiv) was added at room temperature and the stirring was continued for 1 h. The mixture was then quenched with aq. sat. NaCl solution (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by FC on silica gel to afford the target α-methylene-δ-lactam **6**.

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[15] See the Supporting Information for the crystal structure. CCDC-876311 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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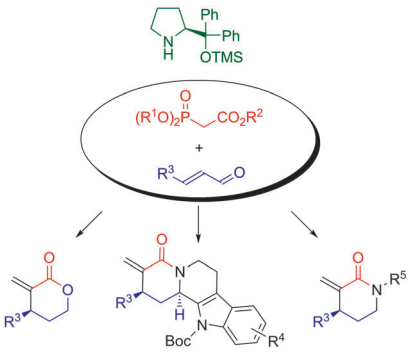
Asymmetric Catalysis



New asymmetric, catalytic protocols for the synthesis of biologically relevant α-methylene-δ-lactones and δ-lactams are described (see scheme). The multi-bond-forming strategies (catalyzed by (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether) involve a Michael addition of trimethyl phosphonoacetate to α,β-unsaturated aldehydes as the key step. The strategy benefits from the diversity of the final products obtained, practicality and broad substrate scope.