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High-yielding sequential one-pot synthesis of chiral and achiral α-substituted acrylates *via* a metal-free reductive coupling reaction†

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A general process for the high-yielding synthesis of substituted chiral and achiral α-substituted acrylates was achieved through the sequential one-pot combination of a metal-free reductive coupling reaction followed by an Eschenmoser methylenation. The proline catalyzed reaction of Meldrum's acid, aldehydes and Hantzsch ester followed by methylenation was successful with Eschenmoser's salt in the presence of an alcohol solvent. Herein, we have shown the high-yielding synthesis of privileged building blocks from chiral/achiral α-substituted acrylates and shown them to be very good intermediates in the pharmaceuticals and natural products synthesis.

Introduction

Much of the current research on organic synthesis is focused on the economy and efficiency of a chemical reaction sequence.[1] The efficiency of a synthetic process depends not only on parameters such as selectivity and reactivity, but also on the overall yield and the number of purification steps. The challenge for synthetic chemists is to synthesize complex target compounds in both high yield and selectivity, and to reduce the number of unit operations, isolations and purification without compromising multi-step one-pot synthesis. In this context, sequential one-pot combination of multi-component and multi-catalysis cascade reactions offers significant advantages over classical linear syntheses by combining a number of sequential reactions in one pot from easily available precursors and catalysts.[1] This concept has become an important tool for organic, medicinal and combinatorial chemists to make high-yielding drugs/natural products and their building blocks with minimum wastage and unit operations.[1]

α-Substituted acrylates are found in many biologically active compounds, pharmaceuticals, and polymer precursors and are also used as key intermediates for the synthesis of α-methylene lactones and lactams, which are found in many natural products and medicinally important molecules (see Fig. 1).[2]

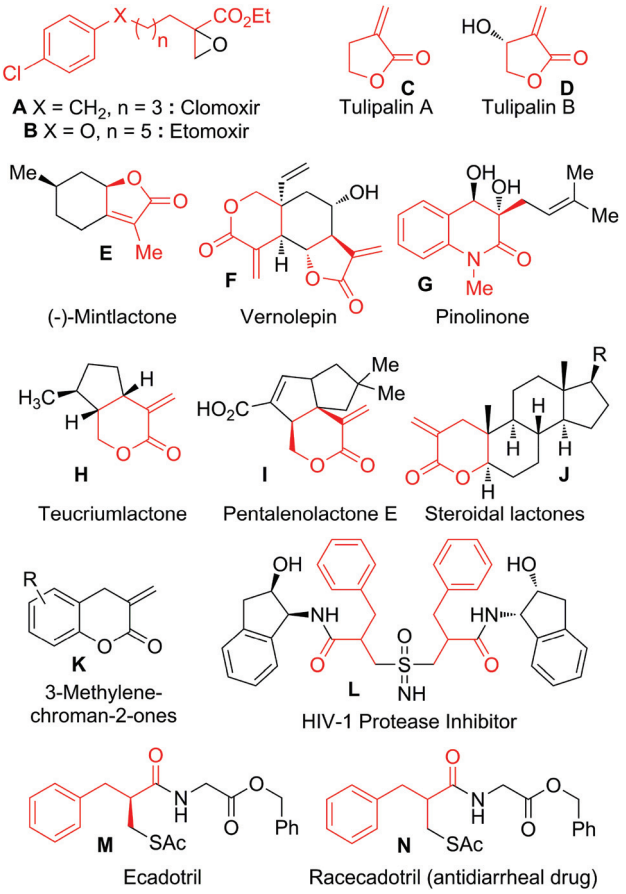

Fig. 1 Medicinal application of methyl α-substituted acrylates.

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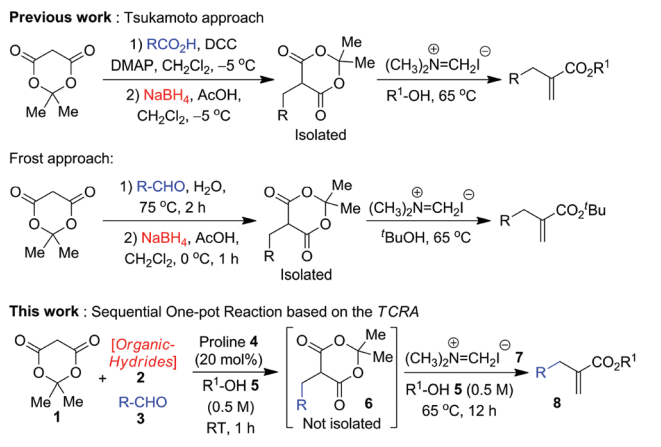
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR, HRMS and HPLC) for all new compounds. See DOI: 10.1039/c4ob00667d

Although many classical synthetic methods (Mannich, Baylis–Hillman, Horner–Wittig and metal catalyzed cross-couplings) have been developed for their synthesis,[3] the development of mild and efficient protocols for the one-pot synthesis of these compounds remains a challenge in modern organic chemistry. In 2002, Tsukamoto *et al.* reported the synthesis of α-substituted acrylates from the corresponding carboxylic acids *via* 5-monosubstituted Meldrum's acids.[4a] Frost *et al.* reported the synthesis of α-substituted *tert*-butyl acrylates starting from the commercially available aldehydes and Meldrum's acids.[4b,c] These two methods suffer from tedious and repetitive work-up and purification steps coupled with unselective $NaBH_4$-mediated olefinic reduction, limited substrate scope and low yields (Scheme 1). To the best of our knowledge, there is no sequential one-pot process for the high-yielding synthesis of chiral and achiral α-substituted acrylates starting from commercially available simple materials. Therefore, the development of a high-yielding sequential one-pot procedure for the synthesis of a variety of α-substituted acrylates is of significant interest (see Scheme 1).

Recently, we have discovered the chemoselective C-alkylation of 1,3-diketones with a variety of aldehydes and organic hydrides under amino acid-catalysis through a three-component reductive alkylation (TCRA) reaction.[5] Since the report of this metal-free reductive coupling or TCRA reaction, many research groups have used this protocol to synthesize high-yielding 2-alkyl-1,3-diketones as a key reaction in their method development towards the total synthesis of natural products and drug molecules.[6,7] Herein, we envisioned that the TCRA reaction of Meldrum's acids **1**, organic hydrides **2** and aldehyde **3** in the presence of a catalytic amount of L-proline **4** would provide the reductive alkylation products **6** at 25 °C, which on further *in situ* treatment with Eschenmoser's salt (*N*,*N*-dimethylmethyleneiminium iodide) **7** in alcohol **5** would provide the α-substituted acrylates **8** in very good yields *via* a domino TCRA/alkylation/methylenation (TCRA/A/M) reaction sequence in a one-pot manner (Scheme 1).



Scheme 1 Synthesis of alkyl α-substituted acrylates through a domino metal-free reductive coupling reaction (TCRA) and Eschenmoser methylenation.

Results and discussion

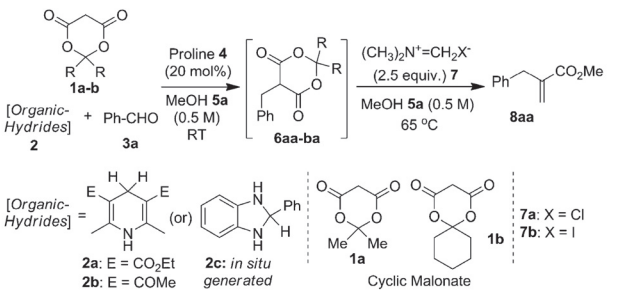
Preliminary optimization of the sequential one-pot TCRA/A/M reaction

The initial investigation looked into the TCRA/A/M between Meldrum's acid **1a** and benzaldehyde **3a** in methanol **5a**. A number of substrates were screened using the proline catalyst including Meldrum's acids **1a–b**, organic-hydrides **2a–c** and Eschenmoser's salts **7a–b** for TCRA/A/M reaction with benzaldehyde **3a** in methanol **5a** (Table 1). The metal-free reductive coupling or TCRA reaction of Meldrum's acid **1a**, Hantzsch ester **2a** and benzaldehyde **3a** under the L-proline **4**-catalysis in methanol **5a** at 25 °C was complete after 2 h and was then *in situ* treated with 2.5 equivalents of *N*,*N*-dimethyl-methyleneiminium chloride **7a** at 65 °C for 12 h to furnish the methyl 2-benzylacrylate **8aa** in 82% yield (Table 1, entry 1). In a similar manner, a TCRA/A/M reaction of **1a**, **2a**, **3a**, and **4** with *N*,*N*-dimethyl-methyleneiminium iodide **7b** in methanol **5a** at 65 °C for 12 h furnished the expected methyl 2-benzyl acrylate **8aa** in 85% yield (Table 1, entry 2). When the sequential one-pot TCRA/A/M reaction was carried out with other substrates like **1b** or **2b–c**, the expected product **8aa** was furnished in poorer yields (Table 1, entries 3–5). From these preliminary results we came to the conclusion that **1a**, **2a** and **7b** were optimal substrates for the TCRA/A/M reaction (Table 1, entry 2).

Solvent effect on the sequential TCRA/A/M reaction

After this preliminary understanding, we proceeded to investigate the scope of the sequential TCRA/A/M reaction of **1a**, **2a**,

Table 1 Reaction preliminary optimization[a]

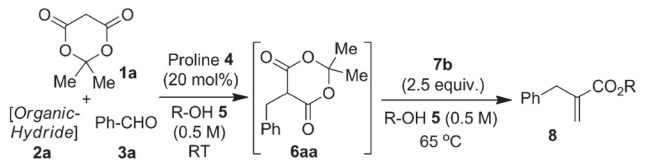


Entry	Cyclic-malonate	Organic-hydride	7	Time (h) TCRA	Time (h) A/M step	Product	Yield[b] (%)
1	**1a**	**2a**	**7a**	2	12	**8aa**	82
2	**1a**	**2a**	**7b**	2	12	**8aa**	85
3	**1b**	**2a**	**7b**	2	12	**8aa**	52
4	**1a**	**2b**	**7b**	2	12	**8aa**	72
5	**1a**	**2c**	**7b**	2	12	**8aa**	62

[a] Reactions were carried out in solvent (0.5 M) with 0.5 mmol of **1a** relative to the **2a** (0.5 mmol) and **3a** (0.5 mmol) in the presence of 20 mol% of L-proline **4** followed by a one-pot alkylation/methylenation (A/M) reaction with 2.5 equiv. of **7** in MeOH **5a** (0.5 M) at 65 °C. [b] Yield refers to the column-purified product.

3a and 7b in various alcoholic solvents 5b–k under the proline-catalysis at 65 °C in order to permit control of the final ester product (Table 2). Sequential one-pot products 8ab–ai were obtained in moderate to good yields by using alcohols 5b–i as solvents (Table 2, entries 2–9). Reaction in *t*-BuOH 5f furnished the expected one-pot product 8af in low yield when compared to other larger alkyl alcohols (Table 2, entry 6). Interestingly, a sequential TCRA/A/M reaction of 1a, 2a, 3a and 7b in (*S*)-ethyl lactate 5j as the solvent furnished the desired optically pure product 8aj in low yield (Table 2, entry 10). This may be due to the moderate steric hindrance of the alkyl portion of (*S*)-ethyl lactate. Surprisingly, a sequential TCRA/A/M reaction of 1a, 2a, 3a and 7b in water furnished the 2-benzylacrylic acid 8ak in 68% yield, which is a better yield compared to the alcoholic solvents investigated excepting the optimal conditions with methanol (Table 2, entries 1 and 11). To further improve the yield of 8aa, we also tested the sequential one-pot TCRA/A/M reaction in a 1 : 1 mixture of MeOH–THF, but the yield did not improve compared to the reaction performed in neat methanol (Table 2, entry 12). Sequential one-pot TCRA/A/M products 8aa–ak are useful intermediates in the synthesis of several biologically important molecules;[2] especially 2-benzylacrylic acid (8ak) is an intermediate for the industrial scale synthesis of an anti-diarrheal drug (racecadotril **N**), a neutral endopeptidase inhibitor (ecadotril **M**), an HIV-1 protease inhibitor (**L**) and an enkephalinase inhibitor (RB-101), highlighting the importance of the TCRA/A/M one-pot approach. The structures of all these one-pot products 8 were confirmed by NMR and mass analysis.

Table 2 Solvent effect on the sequential TCRA/A/M reaction



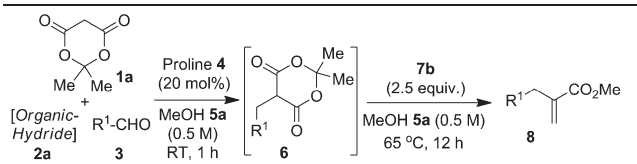
Entry	R-OH	Time (h) TCRA	Time (h) A/M step	Product	Yield[a] (%)
1	MeOH 5a	2	12	8aa	85
2	EtOH 5b	1	12	8ab	42
3	*n*-PrOH 5c	1	12	8ac	60
4	i-PrOH 5d	1	12	8ad	50
5	*n*-BuOH 5e	1	12	8ae	65
6	*t*-BuOH 5f	2	12	8af	37
7	$H_2C{=}CH_2OH$ 5g	1	12	8ag	50
8	$HCCH_2OH$ 5h	1	12	8ah	45
9	BnOH 5i	1	12	8ai	56
10[b]	(*S*)-$CH_3CHOHCO_2Et$ 5j	1	12	8aj	30
11	H_2O 5k	1	12	8ak	68
12	MeOH–THF	12	12	8aa	60

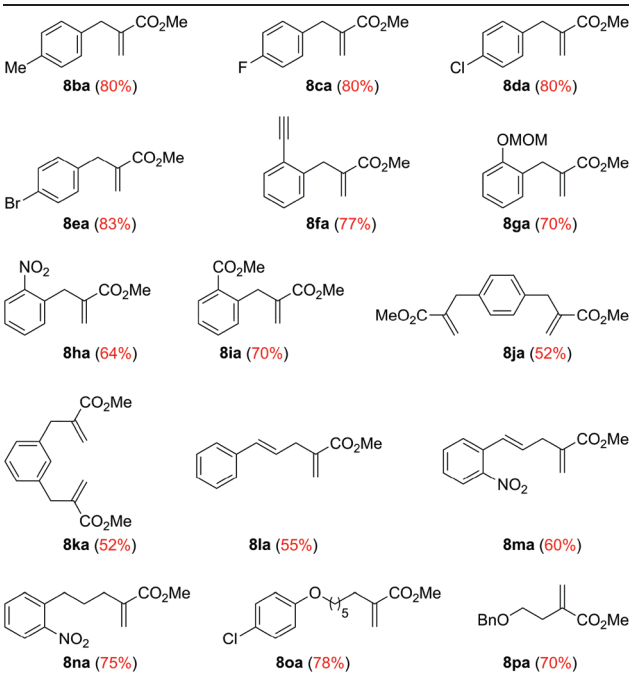
[a] Yield refers to the column-purified product. [b] Reaction performed using (*S*)-ethyl lactate 5j (0.5 M) as a solvent.

Scope of the sequential one-pot TCRA/A/M reaction with achiral aldehydes

With optimised conditions in hand, we explored the scope of the sequential one-pot TCRA/A/M reaction for the synthesis of methyl α-substituted acrylates 8ba–pa by using a variety of aldehydes 3b–p under the proline-catalysis (Table 3). We found that both aryl and alkyl aldehydes proceeded smoothly to afford the expected products 8ba–pa in moderate to very good yields. Interestingly, many of the α-substituted acrylates 8 are not known and this methodology is the first one to prepare them with good yields. For instance, a domino reaction of 4-methylbenzaldehyde 3b with 1a and 2a in methanol 5a under the catalytic amount of proline 4 furnished the TCRA product 6ba, which on *in situ* treatment with 7b gave the corresponding methyl 2-(4-methylbenzyl)acrylate 8ba in 80% yield (Table 3). In a similar manner, products 8ca–ea were obtained in good yields when 4-halobenzaldehydes 3c–e were employed as reactants. A sequential one-pot TCRA/A/M reaction of 2-substituted-benzaldehydes 3f–i also furnished the products 8fa–ia in good yields, despite the steric encumbrance of the *ortho*-substituents (Table 3). The dialdehydes 3j–k were successfully utilized as the substrates in this one-pot reaction to deliver the TCRA/A/M products 8ja–ka in good yields. In addition, the

Table 3 Scope of the sequential one-pot TCRA/A/M reaction with different achiral aldehydes[a]





[a] Yield refers to the column-purified product.

sequential one-pot TCRA/A/M reaction of **1a**, **2a** with aliphatic aldehydes **3l–p** followed by treatment with **7b** in methanol furnished the desired methyl α-substituted acrylates **8la–pa** in good yields (Table 3). Finally, compound **8oa** is an important precursor for the synthesis of the hypoglycemic agent etomoxir (**B**).

Scope of the sequential one-pot TCRA/A/M reaction with chiral aldehydes

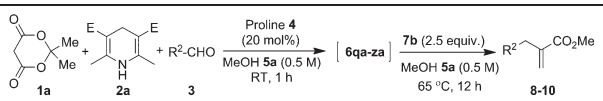
Chiral methyl α-substituted acrylates are important building blocks for the synthesis of medicinally important molecules and also used as attractive intermediates in the total synthesis of natural products and pharmaceuticals.[8] As such the development of mild and simple procedures for the synthesis of these compounds is of significant interest in organic synthesis, and to the best of our knowledge, there is no one-pot procedure for the synthesis of chiral methyl α-substituted acrylates. This methodology may provide a new class of chiral α-substituted methyl acrylates with high enantiomeric purity by employing chiral aldehydes as starting materials.

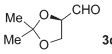
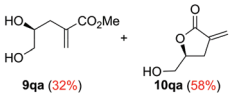
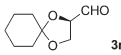
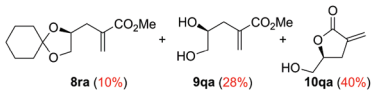
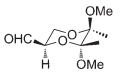
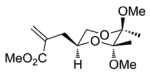
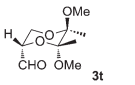
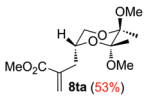
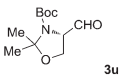
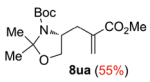
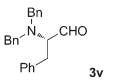
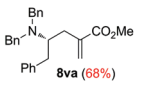
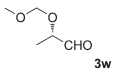
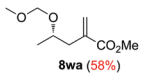
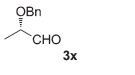
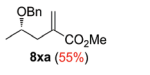
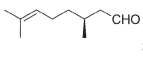
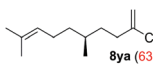
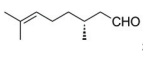
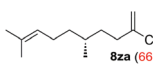
First, we investigated the sequential one-pot reaction of Meldrum's acid **1a**, organic hydride **2a**, and Eschenmoser's salt **7b** with (*R*)-(+)-glyceraldehyde acetonide **3q** under the optimized conditions. Interestingly, we observed the formation of unexpected products (*S*)-methyl 4,5-dihydroxy-2-methylenepentanoate **9qa** and (*S*)-5-(hydroxymethyl)-3-methylenedihydrofuran-2(3*H*)-one **10qa** in 32% and 58% yields respectively instead of the expected product **8qa** (Table 4, entry 1). In a similar manner, the sequential one-pot TCRA/A/M reaction of **1a**, **2a**, **7b** with (*R*)-2,3-cyclohexylideneglyceraldehyde **3r** under the optimized conditions furnished the desired product **8ra** in only 10% yield, which is accompanied by unexpected products **9qa** and **10qa** in 28% and 40% yields, respectively (Table 4, entry 2). The formation of the unexpected products **9qa** and **10qa** can be explained through the *in situ* hydrolysis of the ketal group followed by intramolecular lactonization of **8ra** or **8qa** in the presence of acidic HI, which is *in situ* generated from the reaction. In addition, we performed a sequential one-pot TCRA/A/M reaction of **1a**, **2a**, **7b** with butane-2,3-diacetals of (*R*)-glyceraldehyde and (*S*)-glyceraldehydes (**3s**, **3t**) under the optimized conditions to furnish the desired products **8sa** and **8ta** in 78% and 53% yields, respectively (Table 4, entries 3 and 4).[9] In a similar manner, we have investigated the sequential one-pot reactions by employing a series of chiral aldehydes **3u–3z** under the optimized conditions, and we are happy to find that all reactions proceeded well and the desired products **8ua–8za** were obtained in good yields (Table 4, entries 5–10). All these obtained chiral products **8** have direct applications in medicinal chemistry and natural product synthesis.[2,8]

Synthetic applications of methyl α-substituted acrylates

α-Methylenelactones and α-methylenelactams are important classes of compounds and have received great attention over the past decade in medicinal and synthetic chemistry. Many of the natural and synthetic α-methylenelactones, α-methylenelactams and their analogues have displayed important biological activities (Fig. 1).[2] Although different synthetic methods

Table 4 Scope of the sequential one-pot TCRA/A/M reaction with different chiral aldehydes[a]



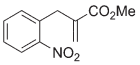
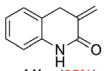
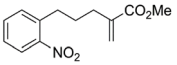
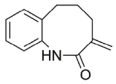
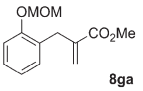
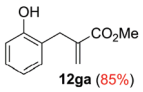
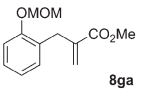
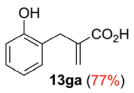
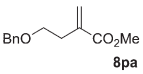
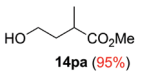
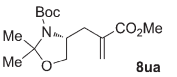
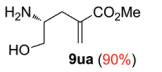
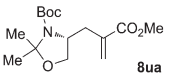
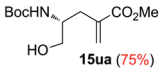
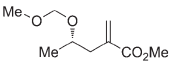
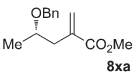
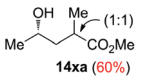
Entry	Chiral aldehyde **3**	Product **8–10**
1	 **3q**	 **9qa** (32%) **10qa** (58%)
2	 **3r**	 **8ra** (10%) **9qa** (28%) **10qa** (40%)
3	 **3s**	 **8sa** (78%)
4	 **3t**	 **8ta** (53%)
5	 **3u**	 **8ua** (55%)
6	 **3v**	 **8va** (68%)
7	 **3w**	 **8wa** (58%)
8	 **3x**	 **8xa** (55%)
9	 **3y**	 **8ya** (63%)
10	 **3z**	 **8za** (66%)

[a] Yield refers to the column-purified product.

have been developed for their synthesis, most of them are lengthy or complicated procedures with harsh reaction conditions.[3,4] Herein, we further utilized the one-pot TCRA/A/M products in the synthesis of biologically important α-methylenelactones, α-methylenelactams and their precursors under suitable reaction conditions (Table 5).

First we focused on the synthesis of 3-methylene-3,4-dihydroquinolin-2(1*H*)-one **11ha** by using methyl 2-(2-nitrobenzyl)acrylate **8ha** as the starting material through a reduction–lactamization sequence in one pot. Nitro group reduction of **8ha** with six equivalents of Fe in CH_3CO_2H at 120 °C for 1 h directly furnished the 3-methylene-3,4-dihydroquinolin-2(1*H*)-one **11ha** in 65% yield (Table 5, entry 1). In a similar manner, reaction of methyl 2-methylene-5-(2-nitrophenyl)pentanoate **8na** under the same reductive lactamization conditions (Fe/CH_3CO_2H) furnished only the corresponding

Table 5 Synthetic applications of methyl α-substituted acrylates[a]

Entry	Substrate **8**	Conditions	Products (**9**–**15**)
1	 **8ha**	Fe/CH_3CO_2H, 120 °C, 1 h	 **11ha** (65%)
2	 **8na**	(i) Fe/CH_3CO_2H, 120 °C, 1 h (ii) ^{t}BuOK, Dry THF, RT, 8 h	 **11na** (57%)
3	 **8ga**	10% HCl ^{i}PrOH : THF, 50 °C, 12 h	 **12ga** (85%)
4	 **8ga**	(i) 10% NaOH, MeOH, 70 °C, 7 h (ii) 10% HCl ^{i}PrOH : THF, 50 °C, 12 h	 **13ga** (77%)
5	 **8pa**	Pd/C (10%) H_2, EtOAc, RT, 2 h	 **14pa** (95%)
6	 **8ua**	MeCOCl MeOH, 70 °C, 2 h	 **9ua** (90%)
7	 **8ua**	*p*-TSA (30%) MeOH, RT, 2 h	 **15ua** (75%)
8	 **8wa**	Conc. HCl MeOH, 70 °C, 1 h	 **10wa** (72%)
9	 **8xa**	Pd/C (10%) H_2, EtOAc, RT, 2 h	 **14xa** (60%)

[a] Yield refers to the column-purified product.

amine product in 66% yield, which on further treatment with 1.2 equiv. of KO^{t}Bu in dry THF at 25 °C for 8 h furnished the cyclized 3-methylene-3,4,5,6-tetrahydrobenzo[*b*]azocin-2(1*H*)-one **11na** in 87% yield for an overall yield of 57% (Table 5, entry 2). For the high-yielding synthesis of 3-methylenechroman-2-one in mind, we prepared two suitable precursors from TCRA/A/M compound **8ga**. Treatment of **8ga** with 10% aqueous HCl in a mixture of i-PrOH : THF at 50 °C for 12 h furnished the corresponding methyl 2-(2-hydroxybenzyl)acrylate **12ga** in 85% yield (Table 5, entry 3). In another route, ester hydrolysis of **8ga** with 10% aqueous NaOH in MeOH at 70 °C for 7 h followed by deprotection of MOM with 10% aqueous HCl in i-PrOH : THF at 50 °C for 12 h furnished the corresponding 2-(2-hydroxybenzyl)acrylic acid **13ga** in 77% yield (Table 5, entry 4). Both the compounds **12ga** and **13ga** are important precursors for the Hutchinson synthesis of 3-methylenechroman-2-one.[10a] Our methodology is simple and mild when compared with the reported Hutchinson protocol for the synthesis of 3-methylenechroman-2-one.[10a] In a similar manner, methyl 4-hydroxy-2-methylbutanoate **14pa** was synthesized in 95% yield using TCRA/A/M product **8pa** *via* a deprotection–reduction sequence under the Pd-mediated hydrogenation with H_2 in EtOAc at 25 °C for 2 h, which is a suitable precursor for the synthesis of 3-methyldihydrofuran-2(3*H*)-one (Table 5, entry 5).

With the inspiration of these results, we were further interested in the synthesis of chiral α-methylene lactones, lactams and their precursors using chiral TCRA/A/M products **8** as shown in Table 5, entries 6–9. Reaction of TCRA/A/M chiral product **8ua** with CH_3COCl in MeOH at 70 °C for 2 h furnished the (*R*)-methyl 4-amino-5-hydroxy-2-methylenepentanoate **9ua** in 90% yield (Table 5, entry 6). Interestingly, treatment of the same substrate **8ua** with 30% *p*-TSA in MeOH at 25 °C for 2 h furnished the (*R*)-methyl 4-((*tert*-butoxycarbonyl)amino)-5-hydroxy-2-methylenepentanoate **15ua** in 75% yield (Table 5, entry 7). Chiral compounds **9ua** and **15ua** could be used as chiral precursors for the asymmetric synthesis of medicinally important five- and six-membered lactams and lactones, respectively. Treatment of TCRA/A/M chiral product **8wa** with conc. HCl in MeOH at 70 °C for 1 h furnished (*S*)-5-methyl-3-methylenedihydrofuran-2(3*H*)-one **10wa** in 72% yield (Table 5, entry 8). Reaction of (*S*)-methyl 4-(benzyloxy)-2-methylenepentanoate **8xa** with H_2 under the Pd-catalysis in EtOAc at 25 °C for 2 h furnished (4*S*)-methyl 4-hydroxy-2-methylpentanoate **14xa** in 60% yield (Table 5, entry 9).

Conclusions

In summary, we have developed a general process for the high-yielding synthesis of substituted chiral and achiral α-substituted acrylates through a sequential one-pot combination of a reductive coupling reaction followed by alkylation and methylenation reactions of Meldrum's acid, Hantzsch ester, aldehydes with Eschenmoser's salt in the presence of a catalytic amount of L-proline. In this manuscript, we have shown the high-yielding synthesis of privileged building blocks from chiral/achiral α-substituted acrylates and have shown them to be useful intermediates in the synthesis of pharmaceuticals and natural products.

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