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High-yielding sequential one-pot synthesis of chiral and achiral α-substituted acrylates *via* 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 sequential one-pot combination of 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 solvents. Herein, we have shown the high-yielding synthesis of privileged building blocks from chiral/achiral α-substituted acrylates and shown them as very good intermediates in the pharmaceuticals and natural products synthesis.

Introduction

Much of the current research in organic synthesis is focused on economy and efficiency of a chemical reaction sequence.[1] The efficiency of a synthetic process not only depends on parameters such as selectivity and reactivity, but also on the overall yield and number of purification steps. The challenge for synthetic chemists is to synthesize complex target compounds both in 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 offer 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 biological active compounds, pharmaceuticals, polymer precursors and 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] 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,4c] These two methods suffer from tedious and repetive 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 high-yielding sequential one-pot procedure for the synthesis of variety of α-substituted acrylates is of significant interest (see Scheme 1).

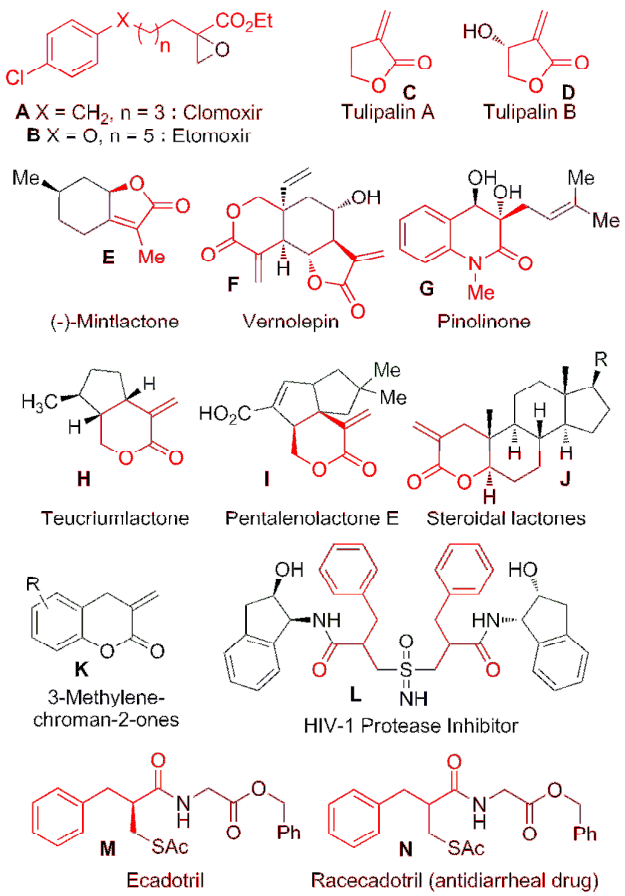

Figure 1 Medicinal application of methyl α-substituted acrylates.

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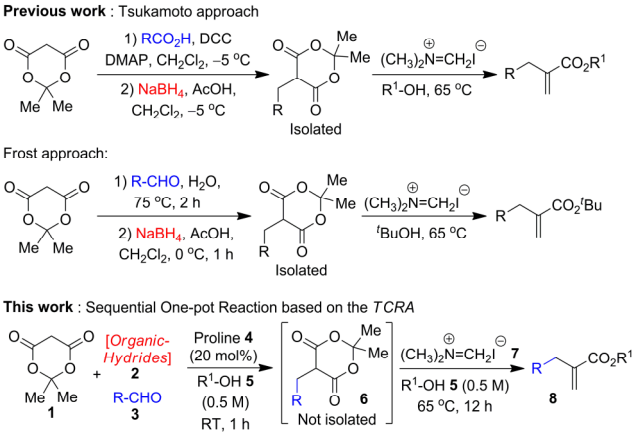
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR, HRMS and HPLC) for all new compounds. See DOI: 10.1039/xxxxxxxx.

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* domino TCRA/alkylation/methylenation (TCRA/A/M) reaction sequence in a one-pot manner (Scheme 1).

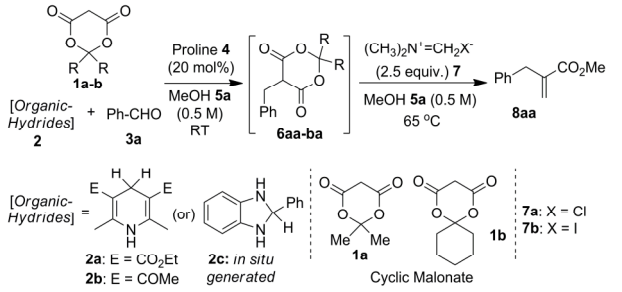


Scheme 1 Synthesis of alkyl α-substituted acrylates through a domino metal-free reductive coupling reaction (TCRA) and Eschenmoser methylenation.

Results and discussion

Preliminary optimization of 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, 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).

Table 1 Reaction preliminary optimization[a]



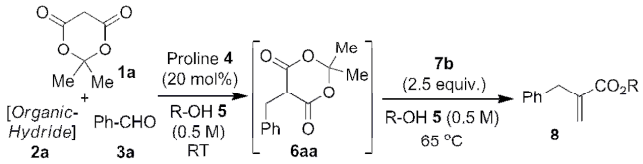
Entry	Cyclic-malonate	Organic-hydride	7	Time (h) TCRA	Time (h) A/M step	Product	Yield (%)[b]
1	**1a**	**2a**	**7a**	2	12	**8aa**	82
2	**1a**	**2a**	**7b**	2	12	**8aa**	85
3	**1b**	**2a**	**7b**	2	12	**8aa**	52
4	**1a**	**2b**	**7b**	2	12	**8aa**	72
5	**1a**	**2c**	**7b**	2	12	**8aa**	62

[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 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.

Solvent effect on the sequential TCRA/A/M reaction: After this preliminary understanding, we proceeded to investigate the scope of sequential TCRA/A/M reaction of **1a**, **2a**, **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 solvent (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, sequential TCRA/A/M reaction of **1a**, **2a**, **3a** and **7b** in (*S*)-ethyl lactate **5j** as solvent furnished the desired optically pure product **8aj** in low yield (Table 2, entry 10). This may be due to the moderate steric hinderence of alkyl portion of (*S*)-ethyl lactate. Surprisingly, 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 anti-diarrheal drug (racecadotril **N**), neutral endopeptidase inhibitor (ecadotril **M**), HIV-1 protease inhibitor (**L**) and enkephalinase inhibitor (RB-101), which is highlighting the

importance of 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



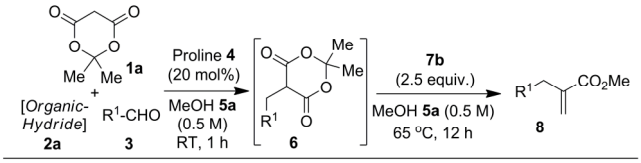
Entry	R-OH	Time (h) TCRA	Time (h) A/M step	Product	Yield (%)[a]
1	MeOH **5a**	2	12	**8aa**	85
2	EtOH **5b**	1	12	**8ab**	42
3	n-PrOH **5c**	1	12	**8ac**	60
4	*i*-PrOH **5d**	1	12	**8ad**	50
5	*n*-BuOH **5e**	1	12	**8ae**	65
6	*t*-BuOH **5f**	2	12	**8af**	37
7	$H_2C{=}CH_2OH$ **5g**	1	12	**8ag**	50
8	$HCCH_2OH$ **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

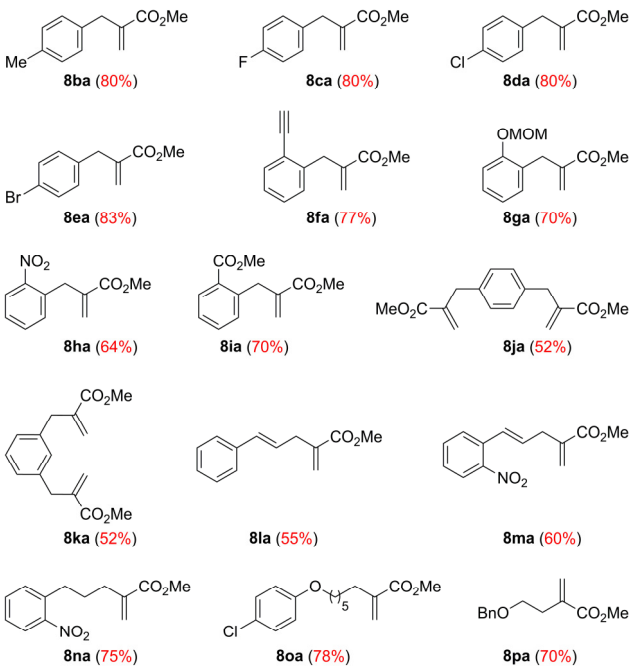
[a] Yield refers to the column-purified product. [b] Reaction performed by using (*S*)-ethyl lactate **5j** (0.5 M) as a solvent.

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

With optimised conditions in hand, we explored the scope of 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, 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. 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 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 hypoglycemic agent etomoxir (**B**).

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.

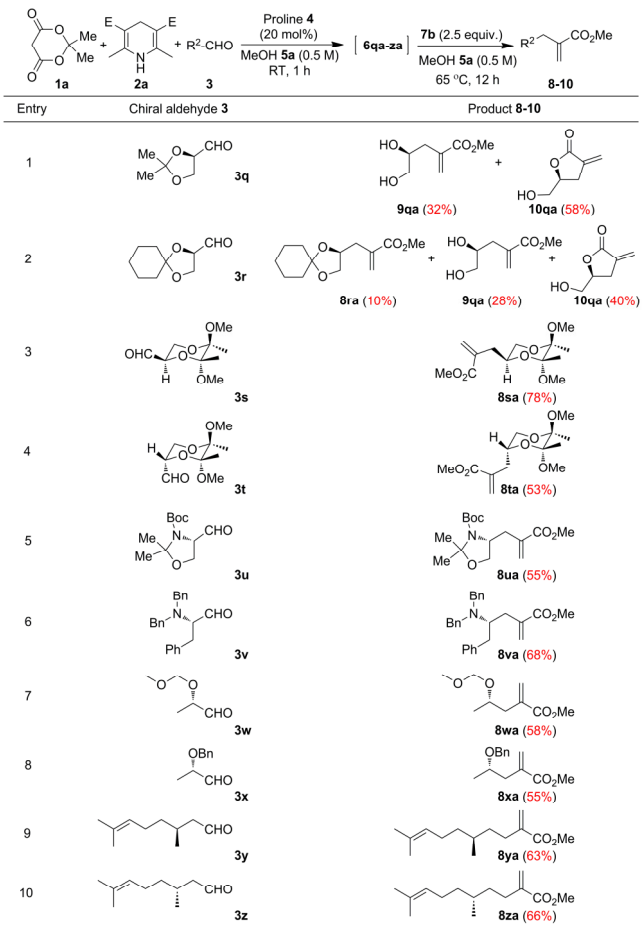
Scope of the sequential one-pot TCRA/A/M reaction with chiral aldehydes:

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 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, 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 with 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 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 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, entry 3, 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, entry 5-10). All these obtained chiral products **8** have direct applications in medicinal chemistry and natural product synthesis.[2,8]

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

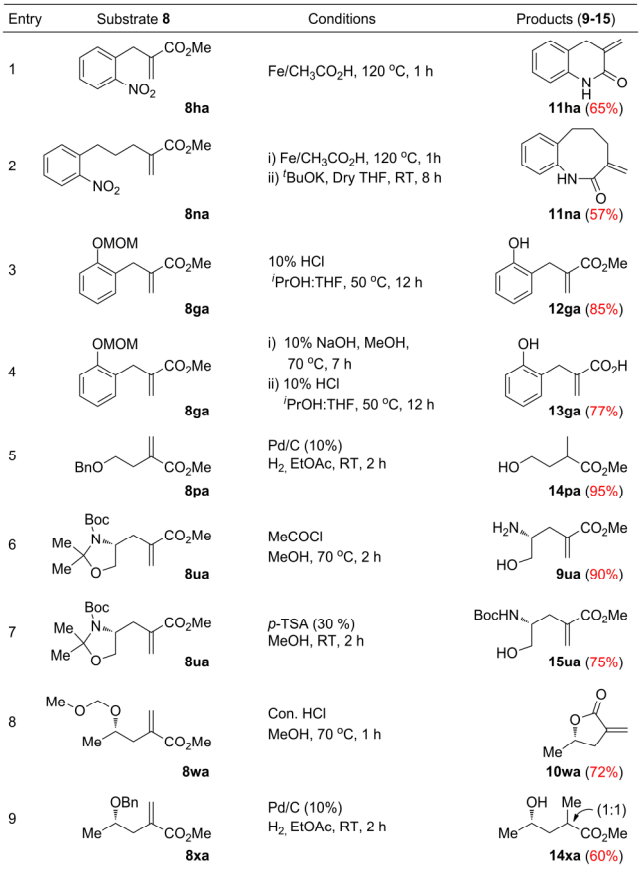


[a] Yield refers to the column-purified product.

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 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 the suitable reaction conditions (Table 5).

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



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

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 equiv. 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 condition (Fe/CH_3CO_2H) furnished only the corresponding 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 to 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 by using TCRA/A/M product **8pa** *via* 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 by 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 a 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 con. 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 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.

Acknowledgements

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References

1 For selected recent reviews on general domino and multi-component reactions, see: (a) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun.,* 2003, 551-564; (b) J. –C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.,* 2005, **105**, 1001-1020; (c) D. J. Ramon and M. Yus, *Angew. Chem. Int. Ed.,* 2005, **44**, 1602-1634; (d) L. F. Tietze, *Chem. Rev.,* 1996, **96**, 115-136; (e) L. F. Tietze and F. Haunert, *Stimulating Concepts in Chemistry* (eds Vogtle, F.; Stoddart, J. F.; Shibasaki, M.) 39-64 (Wiley-VCH, Weinheim, 2000); (f) L. F. Tietze and A. Modi, *Med. Res. Rev.,* 2000, **20**, 304-322; For selected recent reviews on organocatalytic sequential one-pot and domino reactions, see: (g) D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas III, *ACS Catal.*, 2014, **4**, 743–762; (h) H. Jiang, L. Albrecht and K. A. Jørgensen, *Chem. Sci.*, 2013, **4**, 2287-2300; (i) D. B. Ramachary and Y. V. Reddy, *Eur. J. Org. Chem.*, 2012, 865-887; (j) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.,* 2010, **2**, 167– 178; (k) C. F. Barbas III, *Angew. Chem. Int. Ed.,* 2008, **47**, 42-47; (l) A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.,* 2007, **107**, 5416-5470; (m) C. J. Chapman and C. G. Frost, *Synthesis* 2007, 1-21; For selected recent papers on organocatalytic sequential one-pot and domino reactions, see: (n) D. B. Ramachary, Ch. Venkaiah, P. M. Krishna, *Chem. Commun.,* 2012, **48**, 2252-2254; (o) D. B. Ramachary, Y. V. Reddy, A. Banerjee and S. Banerjee, *Org. Biomol. Chem.,* 2011, **9**, 7282-7286; (p) B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.,* 2011, **3**, 473-477; (q) M. Rueping, A. Kuenkel, F. Tato and J. W. Bats, *Angew. Chem. Int. Ed.,* 2009, **48**, 3699-3702; (r) H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem. Int. Ed.,* 2009, **48**, 1304-1307; (s) B. –C. Hong, R. Y. Nimje, A. A. Sadani and J. –H. Liao, *Org. Lett.,* 2008, **10**, 2345-2348; (t) D. B. Ramachary, V. V. Narayana and K. Ramakumar, *Eur. J. Org. Chem.*, 2008, 3907-3911; (u) D. B. Ramachary, G. B. Reddy, and R. Mondal, *Tetrahedron Lett.*, 2007, **48**, 7618-7623; (v) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* 2006, **441**, 861-863; (w) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2005, **127**, 15051-15053; (x) J. W. Yang, M. T. H. Fonseca, B. List, *J. Am. Chem. Soc.,* 2005, **127**, 15036-15037; (y) N. Halland, P. S. Aburel and K. A. Jorgensen, *Angew. Chem. Int. Ed.,* 2004, **43**, 1272-1277; (z) D. B. Ramachary, N. S. Chowdari and C. F. Barbas III, *Angew. Chem. Int. Ed.,* 2003, **42**, 4233-4237; For the process intensification, see: (za) A. A. Desai, E. J. Molitor and J. E. Anderson, *Org. Process Res. Dev.*, 2012, **16**, 160−165.

2 (a) J. Modranka, A. Albrecht, R. Jakubowski, H. Krawczyk, M. Różalski, U. Krajewska, A. Janecka, A. Wyrębska, B. Różalska and T. Janecki, *Bioorg. Med. Chem.*, 2012, **20**, 5017-5026; (b) D. Konkolewicz, A. J. D. Magenau, S. E. Averick, A. Simakova, H. He and K. Matyjaszewski, *Macromolecules* 2012, **45**, 4461−4468; (c) X. Chen, L. Caporaso, L. Cavallo and E. Y. –X. Chen, *J. Am. Chem. Soc.,* 2012, **134**, 7278−7281; (d) T. Mendgen, T. Scholz and C. D. Klein, *Bioorg. Med. Chem. Lett.,* 2010, **20**, 5757-5762; (e) G. M. Miyake, Y. Zhang and E. Y. –X. Chen, *Macromolecules* 2010, **43**, 4902–4908; (f) Y. Hu, X. Xu, Y. Zhang, Y. Chen and E. Y. –X. Chen, *Macromolecules* 2010, **43**, 9328–9336; (g) Y. Zhang, G. M. Miyake and E. Y. –X. Chen, *Angew. Chem. Int. Ed.,* 2010, **49**, 10158–10162; (h) F. –X. Felpin, J. Coste, C. Zakri and E. Fouquet, *Chem. Eur. J.*, 2009, **15**, 7238–7245; (i) N. A. A. Rossi, Y. Zou, M. D. Scott and J. N. Kizhakkedathu, *Macromolecules* 2008, **41**, 5272-5282; (j) D. Lu and R. Vince, *Bioorg. Med. Chem. Lett.,* 2007, **17**, 5614-5619; (k) T. Janecki, E. Błaszczyk, K. Studzian, A. Janecka, U. Krajewska and M. Rozùalski, *J. Med. Chem.,* 2005, **48**, 3516-

3521; (l) T. Janecki, E. Błaszczyk, K. Studzian, M. Rozùalski, U. Krajewska and A. Janecka, *J. Med. Chem.,* 2002**, 45**, 1142-1145; (m) D. Basavaiah and N. Kumaragurubaran, *Tetrahedron Lett.*, 2001, **42**, 477–479; (n) S. S. Jew, E. Y. Roh, E. Y. Baek, L. Mireille, H. O. Kim, B. S. Jeong, M. K. Park and H. G. Park, *Tetrahedron: Asymmetry* 2000, **11**, 3395-3401; (o) W. Adam, P. Groer and C. R. Saha-MoÈ ller, *Tetrahedron: Asymmetry* 2000, **11**, 2239-2243; (p) U. Höller, G. M. König and A. D. Wright, *Eur. J. Org. Chem.,* 1999, 2949-2955; (q) G. T. Crisp and A. G. Meyer, *Tetrahedron* 1995, **51**, 5831-5846; (r) J. W. H. Watthey, J. L. Stanton, M. Desai, J. E. Babiarz and B. M. Finnt, *J. Med. Chem.,* 1985, **28**, 1511-1516; (s) J. Modranka, A. Albrecht, R. Jakubowski, H. Krawczyk, M. Rozalski, U. Krajewska, A. Janecka, A. Wyrebska, B. K. Eistetter, H. P. O. Wolf, *J. Med. Chem*., 1982, **25**, 109-113; (t) P. Barbier and C. Benezra, *J. Med. Chem.,* 1982, **25**, 943-946.

3 (a) P. M. Murray, J. F. Bower, D. K. Cox, E. K. Galbraith, J. S. Parker and J. B. Sweeney, *Org. Process Res. Dev.,* 2013, **17**, 397-405; (b) M. L. N. Rao and S. Giri, *Eur. J. Org. Chem.,* 2012, 4580-4589; (c) Y. –S. Hon, Y. –W. Liu and C. –H. Hsieh, *Tetrahedron* 2004, **60**, 4837-4860.

4 (a) B. Hin, P. Majer and T. Tsukamoto, *J. Org. Chem.,* 2002, **67**, 7365-7368; (b) J. D. Hargrave, G. Bish and C. G. Frost, *Chem. Commun.,* 2006, 4389-4391; (c) C. G. Frost, S. D. Penrose and R. Gleave, *Synthesis* 2009, 627-635.

5 For original papers on the development of organocatalytic reductive coupling or *TCRA* reactions, see for review: (*a*) D. B. Ramachary and S. Jain, *Org. Biomol. Chem.,* 2011, **9**, 1277–1300; For the papers, see: (*b*) D. B. Ramachary and Y. V. Reddy, *J. Org. Chem.,* 2010, **75**, 74–85; (*c*) D. B. Ramachary and M. S. Prasad, *Tetrahedron Lett.,* 2010, **51**, 5246-5251; (*d*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.,* 2010, **8**, 2859-2867; (*e*) D. B. Ramachary, Ch. Venkaiah, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.,* 2009, **7**, 2053-2062; (*f*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.,* 2008, **6**, 4176-4187; (*g*) D. B. Ramachary, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.,* 2008, **6**, 4188-4197; (*h*) D. B. Ramachary, M. Kishor and Y. V. Reddy, *Eur. J. Org. Chem.,* 2008, 975–993; (*i*) D. B. Ramachary and M. Kishor, *J. Org. Chem.,* 2007, **72**, 5056–5068; (*j*) D. B. Ramachary and G. Babul Reddy, *Org. Biomol. Chem.,* 2006, **4**, 4463–4468; (*k*) D. B. Ramachary, M. Kishor and G. Babul Reddy, *Org. Biomol. Chem.,* 2006, **4**, 1641-1646; (*l*) D. B. Ramachary, M. Kishor and K. Ramakumar, *Tetrahedron Lett.,* 2006, **47**, 651-656.

6 For the application of organocatalytic reductive coupling or *TCRA* reaction in drugs/drug-like molecules synthesis, see: (a) N. D. Ide, J. A. Ragan, G. Bellavance, S. J. Brenek, E. M. Cordi, G. O. Jensen, K. N. Jones, D. LaFrance, K. R. Leeman, L. J. Letendre, D. Place, C. L. Stanchina, G. W. Sluggett and H. Strohmeyer, *Org. Process Res. Dev.,* 2014, **18**, 45−56; (b) Y. –C. Wong, C. –T. Tseng, T. –T. Kao, Y. –C. Yeh and K. –S. Shia, *Org. Lett.*, 2012, **14**, 6024-6027; (*c*) C. Ballatore, J. H. Soper, F. Piscitelli, M. James, L. Huang, O. Atasoylu, D. M. Huryn, J. Q. Trojanowski, V. M. –Y. Lee, K. R. Brunden and A. B. Smith III, *J. Med. Chem.,* 2011, **54**, 6969-6983; (d) J. Tummatorn and G. B. Dudley, *Org. Lett.*, 2011, **13**, 1572-1575; (e) L. Li, W. K. S. Chua, *Tetrahedron Lett.*, 2011, **52**, 1392–1394; (f) D. B. Ramachary, R. Mondal and Ch. Venkaiah, *Org. Biomol. Chem.,* 2010, **8**, 321–325; (*g*) D. B. Ramachary, R. Mondal and Ch. Venkaiah, *Eur. J. Org. Chem.,* 2010, 3205–3210; (h) D. B. Ramachary, Y. V. Reddy and B. Veda Prakash, *Org. Biomol. Chem.*, 2008, **6**, 719-726.

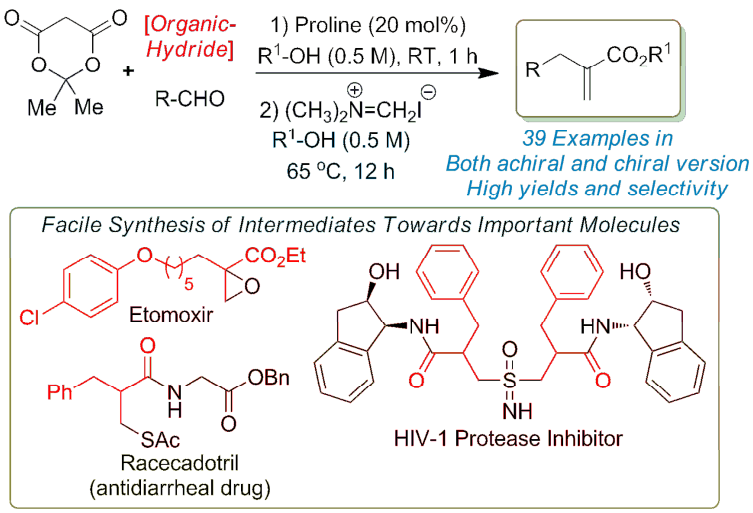
7 For the application of organocatalytic reductive coupling or *TCRA* reaction in the total synthesis of natural products, see: (*a*) E. Elamparuthi, C. Fellay, M. Neuburger and K. Gademann, *Angew. Chem. Int. Ed.,* 2012, **51**, 4071-4073; (*b*) K. Hiroya, Y. Suwa, Y. Ichihashi, K. Inamoto, and T. Doi, *J. Org. Chem.,* 2011, **76**, 4522-4532; (c) L. Miao, H. Shu, A. R. Noble, S. P. Fournet, E. D. Stevens and M. L. Trudell, *Arkivoc,* 2010, **4**, 6-14; (d) K. Hiroya, Y. Ichihashi, Y. Suwa, T. Ikai, K. Inamoto and T. Doi, *Tetrahedron Lett.,* 2010, **51**, 3728-3731; (e) P. K. Amancha, H. –J. Liu, T. W. Ly and K. –S. Shia, *Eur. J. Org. Chem.,* 2010, 3473–3480; (f) K. Hiroya, Y. Ichihashi, A. Furutono, K. Inamoto, T. Sakamoto and T. Doi, *J. Org. Chem.,* 2009, **74**, 6623-6630.

8 (a) J. E. Beddow, S. G. Davies, K. B. Ling, P. M. Roberts, A. J. Russell, A. D. Smith and J. E. Thomson, *Org. Biomol. Chem.,* 2007, **5**, 2812-2825; (b) H. –S. Lee, J. –S. Park, B. M. Kim and S. H. Gellman, *J. Org. Chem.,* 2003, **68**, 1575-1578; (c) O. Ouerfelli, M. Ishida, H.Shinozaki, K. Nakanishi and Y. Ohfune, *Synlett* 1993, 409-410.

9 For the preparation and application of butane-2,3-diacetals of glyceraldehydes, see: (a) P. Michel and S. V. Ley, *Angew. Chem. Int. Ed.,* 2002, **41**, 3898-3901; (b) K. R. Knudsen, A. F. Stepan, P. Michel and S. V. Ley, *Org. Biomol. Chem.*, 2006, **4**, 1471-1473; (c) K. L. Bridgwood, C. C. Tzschucke, M. O'Brien, S. Wittrock, J. M. Goodman, J. E. Davies, A. W. J. Logan, M. R. M. Hüttl and S. V. Ley, *Org. Lett.*, 2008, **10**, 4537–4540.

10 (a) A. D. Harmon and C. R. Hutchinson, *J. Org. Chem.*, 1975, **40**, 3474-3480; (b) B. Alcaide, G. Esteban, Y. Martin-Cantalejo, J. Plumet and J. Rodn'guez-Lopez, *J. Org. Chem.,* 1994, **59**, 7994-8002; (c) S. Gowrisankar, K. Y. Lee and J. N. Kim, *Bull. Korean Chem. Soc*., 2007, **28**, 624-628; (d) A. Albrecht, F. Morana, A. Fraile and K. A. Jørgensen, *Chem. Eur. J.*, 2012, **18**, 10348–10354; (e) X. Companyó, P. –Y. Geant, A. Mazzanti, A. Moyano and R. Rios, *Tetrahedron* 2014, **70**, 75-82.

Graphical Abstract for Table of Contents:



Short Statement

A variety of chiral and achiral α-substituted acrylates were furnished in very good yields with excellent selectivity by using an organocatalytic reductive coupling reaction (TCRA) followed by Eschenmoser methylenation.