JOC Article
pubs.acs.org/joc

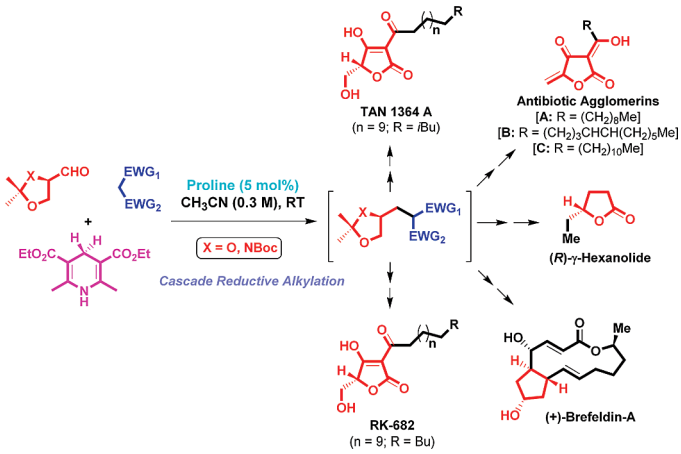
A General Approach to Chiral Building Blocks via Direct Amino Acid-Catalyzed Cascade Three-Component Reductive Alkylations: Formal Total Synthesis of HIV-1 Protease Inhibitors, Antibiotic Agglomerins, Brefeldin A, and (*R*)-γ-Hexanolide

Dhevalapally B. Ramachary* and Y. Vijayendar Reddy

School of Chemistry, University of Hyderabad, Central University (PO), Hyderabad 500 046, India

ramsc@uohyd.ernet.in

Received August 20, 2009



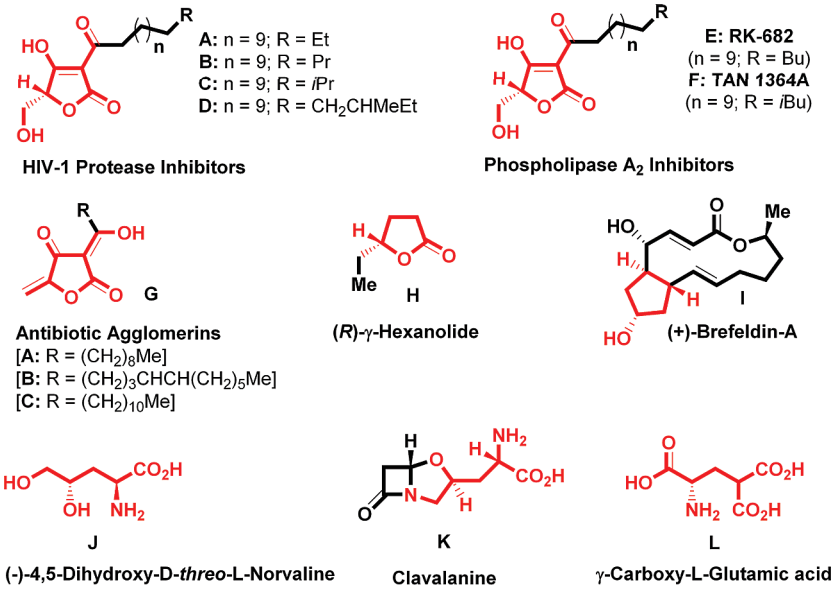
Multicatalysis cascade (MCC) process for the synthesis of highly substituted chiral building blocks (2-alkyl-CH-acids, 2-alkylcyclohexane-1,3-diones, 2-alkylcyclopentane-1,3-diones, and H−P ketone analogues) is presented based on the cascade three-component reductive alkylation's (TCRA) platform. Herein, we developed the high-yielding alkylation of a variety of CH-acids with (*R*)-glyceraldehyde acetonide/(*S*)-Garner aldehyde and Hantzsch ester through amino acid-catalyzed TCRA reaction without racemization at the α-position to carbonyl. Direct sequential combination of the L-proline-catalyzed TCRA reaction with other reactions like cascade alkylation/ketenization/esterification (A/K/E), alkylation/ketenization/esterification/alkylation (A/K/E/A), Brønsted acid-catalyzed cascade hydrolysis/lactonization/esterification (H/L/E), hydrolysis/esterification (H/E), hydrolysis/oxy-Michael/dehydration (H/OM/DH), and Robinson annulation (RA) of CH-acids, chiral aldehydes, Hantzsch ester, diazomethane, methyl vinyl ketone, various active olefins, and acetylenes furnished the highly functionalized chiral building blocks in good to high yields with excellent diastereoselectivities. In this context, many of the pharmaceutically applicable chiral building blocks were prepared via MCC reactions.

Introduction

(*R*)-Glyceraldehyde acetonide and (*S*)-Garner aldehyde derivatives from olefination/hydrogenation are an important class of heterocycles and very good chiral building blocks which display a very large spectrum of biological/chemical activities and are widely used as drug intermediates and ingredients in pharmaceuticals and also in the total synthesis of natural products (see Chart 1).[1] As such, the development of more general catalytic asymmetric methods for their preparation is of significant interest.[2] For example, diethyl 2-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)malonate was utilized as key intermediate in the total synthesis of natural products like HIV-1 protease inhibitors **A**−**D**, phospholipase A_2 inhibitors **E** and **F**, antibiotic agglomerins **G**,

Published on Web 12/02/2009 DOI: 10.1021/jo901799n

CHART 1. Natural Products Library Generated from (*R*)-Glyceraldehyde Acetonide and (*S*)-Garner Aldehyde Derivatives



(*R*)-γ-hexanolide **H**, and (+)-brefeldin-A **I** but which was prepared only in 40% overall yield from four steps starting from (*R*)-glyceraldehyde acetonide (see eq 1).[1a−i] Interestingly, to the best of our knowledge, there is no report on the direct catalytic asymmetric single step method for the synthesis of functionalized dialkyl 2-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)malonates and dialkyl 2-(3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-ylmethyl)malonates, which are good intermediates for the synthesis of biologically active natural products as demonstrated in this work (see Chart 1). Herein, we reported the organocatalytic single step approach to the asymmetric synthesis of functionalized chiral building blocks based on (*R*)-glyceraldehyde acetonide and (*S*)-Garner aldehyde via "three-component reductive alkylation reactions".[3a−c]

Recently, we discovered the amino acid-catalyzed three-component reductive alkylation reactions of ketones/aldehydes with a variety of CH-acids and Hantzsch ester to provide a general route to a variety of alkylation products in good yields with high chemoselectivity, which is known as the "three-component reductive alkylation (TCRA)" reaction.[3a−c] The advent of amino acid-catalyzed TCRA reaction technology triggered a burst of activity in the synthesis of a huge variety of alkylation products through biomimetic iminium-catalysis chemistry for the 1 × C−C and 2 × C−H bond formations and also providing high

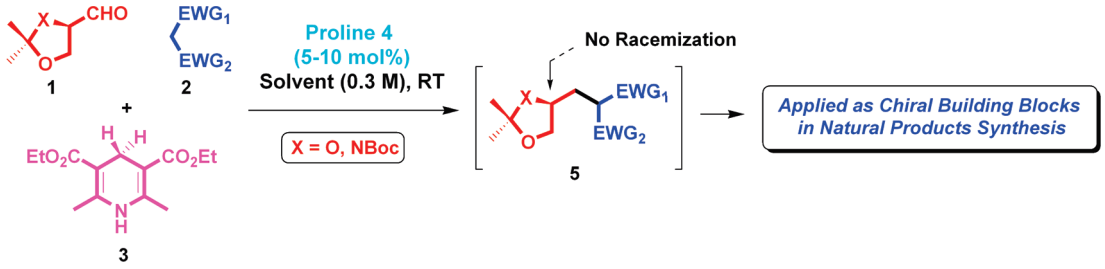
(1) (a) Yamashita, M.; Murai, H.; Mittra, A.; Yoshioka, T.; Kawasaki, I.; Gotoh, M.; Higashi, T.; Hatsuyama, R.; Ohta, S. *Heterocycles* **1998**, *48*, 2327–2337. (b) Schobert, R.; Jagusch, C. *J. Org. Chem.* **2005**, *70*, 6129–6132. (c) Zhdankina, G. M.; Serebryakov, É. P. *Russ. Chem. Bull.* **1985**, *34*, 2414–2415. (d) Kitahara, T.; Mori, K. *Tetrahedron* **1984**, *40*, 2935–2944. (e) Ariza, J.; Font, J.; Ortuno, R. M. *Tetrahedron Lett.* **1991**, *32*, 1979–1982. (f) Kotkar, S. P.; Suryavanshi, G. S.; Sudalai, A. *Tetrahedron: Asymmetry* **2007**, *18*, 1795–1798. (g) Uchida, I.; Ezaki, M.; Shigematsu, N.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 1342–1344. (h) Bernardo, S. D.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3457–3462. (i) Sodeoka, M.; Sarape, R.; Kagamizono, T.; Osada, H. *Tetrahedron Lett.* **1996**, *37*, 8775–8778. (j) Ray, N. C.; et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4901–4905. (k) Huntington, K. M.; Yi, T.; Wei, Y.; Pei, D. *Biochemistry* **2000**, *39*, 4543–4551. (l) Lu, D.; Vince, R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5614–5619. (m) Anderluh, P. S.; Anderluh, M.; Ilaš, J.; Mravljak, J.; Dolenc, M. S.; Stegnar, M.; Kikelj, D. *J. Med. Chem.* **2005**, *48*, 3110–3113. (n) Wu, Z.; Minhas, G. S.; Wen, D.; Jiang, H.; Chen, K.; Zimniak, P.; Zheng, J. *J. Med. Chem.* **2004**, *47*, 3282–3294. (o) Bohme, T. M.; Keim, C.; Kreutzmann, K.; Linder, M.; Dingermann, T.; Dannhardt, G.; Mutschler, E.; Lambrecht, G. *J. Med. Chem.* **2003**, *46*, 856–867. (p) Howard, J. B.; Nelsestuen, G. L. *Biochem. Biophys. Res. Commun.* **1974**, *59*, 757–763. (q) Nelsestuen, G. L.; Zytkovicz, T. H. *J. Biol. Chem.* **1974**, *249*, 6347–6350. (r) Zytkovicz, T. H.; Nelsestuen, G. L. *J. Biol. Chem.* **1975**, *250*, 2968–2972. (s) Stenflo, J.; Fernlund, P.; Egan, W.; Roepstorff, P. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 2730–2733. (t) Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065–4068. (u) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.

(2) (a) Jiang, S.; Lai, C. C.; Kelley, J. A.; Roller, P. P. *Tetrahedron Lett.* **2006**, *47*, 23–25. (b) Quaedflieg, P. J. L. M.; Kesteleyn, B. R. R.; Wigerinck, P. B. T. P.; Goyvaerts, N. M. F.; Vijn, R. J.; Liebregts, C. S. M.; Kooistra, J. H. M. H.; Cusan, C. *Org. Lett.* **2005**, *7*, 5917–5920. (c) Suarez, R. M.; Sestelo, J. P.; Sarandeses, L. A. *Chem.—Eur. J.* **2003**, *9*, 4179–4187. (d) Ngai, M. −Y.; Kong, J. −R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063–1072. (e) Krief, A.; Dumont, W.; Baillieul, D. *Tetrahedron Lett.* **2005**, *46*, 8033–8035. (f) Kesteleyn, B. R. R.; Surleraux, D. L. N. G. *PCT Int. Appl.* **2003**, 47 pp. CODEN: PIXXD2 WO 2003022853 A1 20030320, CAN 138:238003 (patent written in English). (g) Krief, A.; Provins, L.; Froidbise, A. *Synlett* **1999**, 1936–1938. (h) Ma, D.; Cao, Y.; Yang, Y.; Cheng, D. *Org. Lett.* **1999**, *1*, 285–287.

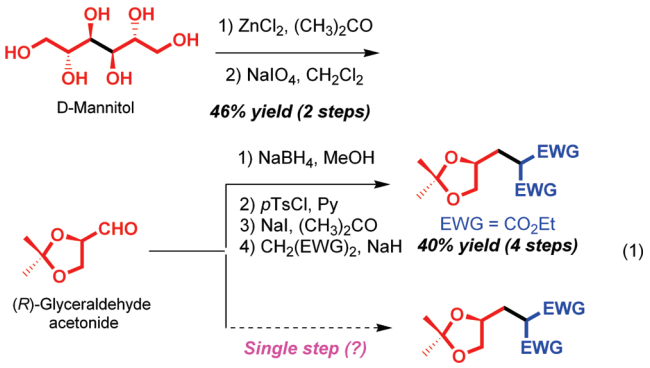
(3) For recent papers on organocatalytic TCRA reactions for C−C/C−H bond formation, see: (a) Ramachary, D. B.; Kishor, M. *J. Org. Chem.* **2007**, *72*, 5056–5068. (b) Ramachary, D. B.; Kishor, M. *Org. Biomol. Chem.* **2008**, *6*, 4176–4187. (c) Ramachary, D. B.; Venkaiah, C.; Reddy, Y. V.; Kishor, M. *Org. Biomol. Chem.* **2009**, *7*, 2053–2062. For recent papers on organocatalytic reductions for C−H bond formation, see: (d) Yang, J. W.; Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660–6662. (e) Yang, J. W.; Fonseca, M. T. H.; Vignola, N.; List, B. *Angew. Chem Int. Ed.* **2005**, *44*, 108–110. (f) Mayer, C.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193–4195. (g) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368–13369. (h) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32–33. (i) Tuttle, J. B.; Quellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662–12663. For recent papers on organocatalytic reductions for C−N bond formation, see: (j) Hofmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424–7426. (k) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84–86. (l) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781–3783. (m) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751–6755. (n) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327–1339. (o) You, S. −L. *Chem. Asian. J.* **2007**, *2*, 820–827. For recent papers on organocatalytic reductions for C−O bond formation, see: (p) Yang, J. W.; List, B. *Org. Lett.* **2006**, *8*, 5653–5655.

(4) For the recent papers on observation of organocatalytic racemization/epimerizations, see: (a) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F. III. *Tetrahedron Lett.* **2002**, *43*, 9591–9595. (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. III. *Synlett* **2003**, *12*, 1910–1914. (c) Ramachary, D. B.; Anebouselvy, K.; Chowdari, N. S.; Barbas, C. F. III. *J. Org. Chem.* **2004**, *69*, 5838–5849. (d) Couturier, C.; Liron, M.; Schlama, T.; Zhu, J. *Synlett* **2005**, *5*, 851–853. (e) Ramachary, D. B.; Reddy, Y. V.; Prakash, B. V. *Org. Biomol. Chem.* **2008**, *6*, 719–726.

SCHEME 1. Direct Amino Acid-Catalyzed Cascade Three-Component Reductive Alkylations



inspiration to develop cellular type cascade reactions based on TCRA platform.[3]



However, the amino acid-catalyzed TCRA reaction of CH-acids **2** and Hantzsch ester **3** with functionalized (*R*)-glyceraldehyde acetonide/(*S*)-Garner aldehyde **1** is not known, but resulting TCRA products **5** have a wide range of applications in pharmaceutical chemistry (see eq 1 and Scheme 1). There is no direct methodology available to prepare **5** by using the classical reaction strategies in a single step. Herein, we have reported a metal-free and green technology for the synthesis of highly substituted (*R*)-glyceraldehyde acetonide and (*S*)-Garner aldehyde derivatives **5** using organocatalytic TCRA reactions from commercially available chiral aldehydes **1**, CH-acids **2**, Hantzsch ester **3**, and amines/amino acid **4** (Scheme 1). In this paper, we discovered the observation of no racemization at the α-position to carbonyl at the normal amino acid-catalyzed TCRA reaction conditions.[4]

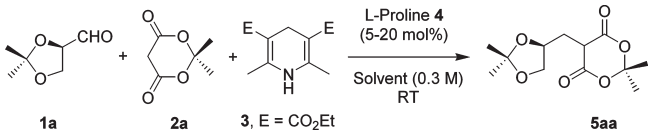
Over the last 5 years, we have been interested in an amino acid mediated multicatalysis cascade (MCC) reactions from multiple components and multiple catalysts for the generation of highly functionalized druglike molecules through C−C, C−H, C−O, and C−N bonds formation in one pot.[5i−k] During our investigation for new reactive species for such MCC processes, we have decided to explore the potential ability of the chiral aldehydes **1** to participate in an amino acid-catalyzed TCRA reaction with CH-acids **2** and Hantzsch ester **3** (see Scheme 1). We imagine that the reaction of (*R*)-glyceraldehyde acetonide **1a** (>98% ee) with Meldrum's acid **2a** and Hantzsch ester **3** under L-proline catalysis may lead to racemic 5-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl[1,3]dioxane-4,6-dione **5aa**. However, TCRA product **5aa** could not be racemized and instead it is shown the >98% ee (based on HPLC analysis) under the standard reaction conditions. This unexpected result represents a good methodology for the preparation of chiral TCRA products and a new reactivity for amino acid catalysts. Herein, we report our findings regarding these TCRA reactions.

Results and Discussion

Three-Component Reductive Alkylation of (*R*)-Glyceraldehyde Acetonide: Reaction Optimization. We initiated our preliminary studies of the TCRA reactions by screening a number of protic/aprotic solvents for the olefination/hydrogenation (O/H) of (*R*)-glyceraldehyde acetonide **1a** with Meldrum's acid **2a** and Hantzsch ester **3** under L-proline **4**-catalysis, and some representative results are shown in Table 1. Interestingly, reaction of (*R*)-**1a** (>98% ee) with 1 equiv each of **2a** and **3** in CH_2Cl_2 under 5 mol % of **4**-catalysis furnished the TCRA product **5aa** in 91% yield with >98% ee (based on HPLC analysis of (−)-**5aa** derivative; see the Supporting Information for more information) after 2.5 h (Table 1, entry 1). The same reaction in CH_2Cl_2 under 10 mol % of L-proline **4**-catalysis furnished the TCRA product **5aa** with increased yield (98%) and similar ee ($[\alpha]^{25}_D = -24.4$) after 2.5 h (Table 1, entry 2). Interestingly, increasing the catalyst loading from 10 to 20 mol %; yield and ee of the TCRA product **5aa** is affected negatively as shown in Table 1, entry 3. The same TCRA reaction in DCE solvent under 10 mol % of L-proline **4**-catalysis furnished the TCRA product **5aa** as similar to CH_2Cl_2 (Table 1, entry 4). Interestingly, TCRA reaction of (*R*)-**1a**, **2a**, and **3** under 10 mol % of **4**-catalysis in CH_3CN for 1 h furnished the

(5) For recent reviews on organocatalytic cascade and multicomponent reactions, see: (a) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143–2173. (c) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1–21. (d) Gerencser, J.; Dorman, G.; Darvas, F. *QSAR Comb. Sci.* **2006**, *25*, 439–448. (e) Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693–700. (f) Enders, D.; Grondal, C.; Huettl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (g) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470. (h) Notz, W.; Tanaka, F.; Barbas, C. F. III. *Acc. Chem. Res.* **2004**, *37*, 580–591. For selected recent papers on organocatalytic cascade reactions from our group, see: (i) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *J. Org. Chem.* **2007**, *72*, 1458–1463. (j) Ramachary, D. B.; Sakthidevi, R. *Chem.—Eur. J.* **2009**, *15*, 4516–4522. For selected recent papers on organocatalytic cascade reactions from other research groups, see: (k) Ramachary, D. B.; Barbas, C. F. III. *Chem.—Eur. J.* **2004**, *10*, 5323–5331. (l) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037. (m) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053. (n) Marigo, M.; Bertelsen, S.; Landa, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475–5479. (o) Enders, D.; Huettl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863. (p) Rios, R.; Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 8679–8682. (q) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354–10355. (r) Tejedor, D.; Gonzalez-Cruz, D.; Santos-Exposito, A.; Marrero-Tellado, J. J.; de Armas, P.; Garcia-Tellado, F. *Chem.—Eur. J.* **2005**, *11*, 3502–3510. (s) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683–3686. (t) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304–1307. (u) Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, X.; Zhong, G. *Org. Lett.* **2008**, *10*, 4585–4588.

TABLE 1. Preliminary Studies on Reductive Alkylation of (*R*)-Glyceraldehyde Acetonide[a]



entry	proline **4** (mol %)	solvent (0.3 M)	time (h)	conversion[b] (%)	yield[c] (%)	specific rotation ($[\alpha]^{25}_D$)[d]
1	5	CH_2Cl_2	2.5	>99	91	−24.6
2	10	CH_2Cl_2	2.5	>99	98	−24.4
3	20	CH_2Cl_2	0.75	>99	91	−23.6
4	10	$(CH_2)_2Cl_2$	2.0	>99	91	−24.4
5	10	CH_3CN	1.0	>99	95	−24.0
6	10	DMF	2.0	>99	87	−22.6
7	10	DMSO	3.0	>99	78	−22.7
8	10	EtOH	1.0	>99	91	−11.9
9[e]		H_2O	72.0	>95	<5	
10[f]	**10**	**CH_3CN**	**8→9**	**80**	**68**	**−24.4**

[a]Reactions were carried out in solvent (0.3 M) with 1.0 equiv each of **2a** and **3** relative to the **1a** (0.5 mmol) in the presence of 5−20 mol % of catalyst **4**. [b]Conversation is based on ^{1}HNMR/TLC analysis. [c]Yield refers to the column-purified product. [d]Specific rotation of all entries determined as 1.0 g/100 mL in $CHCl_3$. [e]Only olefination product 5-(2,2-dimethyl[1,3]dioxolan-4-ylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione (**6aa**) is formed. [f]Reaction performed in sequential manner.

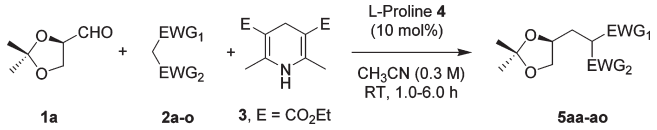
product **5aa** in 95% yield with sustained ee ($[\alpha]^{25}_D = -24.0$) as shown in Table 1, entry 5. But, L-proline **4**-catalyzed TCRA reaction of **1a**, **2a**, and **3** in DMF/DMSO solvents for 2/3 h furnished the product **5aa** in 87/78% yield with decreased ee ($[\alpha]^{25}_D = -22.6$) as shown in Table 1, entries 6 and 7, respectively. Surprisingly, L-proline **4**-catalyzed TCRA reaction of **1a**, **2a**, and **3** in EtOH solvent for 1 h furnished the product **5aa** in 91% yield with almost ≤50% ee ($[\alpha]^{25}_D = -11.9$) as shown in Table 1, entry 8. This provides strong evidence that enantiomerically pure (*R*)-glyceraldehyde acetonide **1a** is racemizing through iminium-catalysis in protic solvents like ethanol in the process of TCRA reaction.[4] The solvent promoted one-pot TCRA reaction of **1a**, **2a**, and **3** in H_2O without catalyst furnished the expected product **5aa** in <5% conversion, but the olefination is completed with >95% yield under green reaction conditions (Table 1, entry 9). Interestingly, performing the TCRA reaction in a sequential one-pot manner was took longer reaction times (8 h for olefination and 9 h for hydrogenation) with only ≤80% conversion and with sustained ee ($[\alpha]^{25}_D = -24.4$) as shown in Table 1, entry 10, this may be due to the autocatalytic nature of the Hantzsch ester **3** in the cascade TCRA (olefination−hydrogenation) reaction.[3a−c] The optimized conditions for the TCRA reaction of **1a**, **2a**, and **3** in CH_3CN or CH_2Cl_2 at 25 °C to furnish **5aa** with excellent conversions and without racemization required the presence of the catalytic amount of amino acid **4** (entries 1−5).

Diversity-Oriented Chiral Synthesis of TCRA Products 5aa−ao. With an efficient amino acid-catalyzed TCRA protocol in hand, the scope of the L-proline-catalyzed TCRA reactions were investigated with various CH-acids **2a−o**. A series of cyclic and acyclic CH-acids **2a−o** were reacted with each 1.0 equiv of (*R*)-glyceraldehyde acetonide **1a** and Hantzsch ester **3** catalyzed by 10 mol % of L-proline **4** at 25 °C for 1−6 h in CH_3CN (Table 2). The (*S*)-5-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl[1,3]dioxane-4,6-dione **5aa** and (*S*)-5-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-2,2-dialkyl[1,3]dioxane-4,6-diones **5ab−ac** were obtained as enantiomerically pure with excellent yields. The reaction of (*R*)-**1a** and **3** with barbituric acid **2d** and *N*,*N*-dimethylbarbituric acid **2e** furnished the chiral TCRA products **5ad** and **5ae** as single enantiomers in good yields (Table 2). (*S*)-2-(2,2-Dimethyl[1,3]dioxolan-4-ylmethyl)-cyclohexane-1,3-dione **5ag**, and related chiral TCRA products **5ah−ak** were generated as single enantiomers with excellent yields from (*R*)-**1a**, **2g−k**, and **3** at 25 °C under L-proline-catalysis and which are very good starting materials for steroid drug analogue synthesis (Table 2; see the Supporting Information for HPLC analysis of **5af** derivative).[3a,b] The reaction of (*R*)-**1a** and **3** with acyclic CH-acids **2l−o** under L-proline-catalysis at 25 °C for 1−6 h in CH_3CN furnished the chiral TCRA products **5al−ao** as single enantiomers in 2:1 to 1:1 dr ratio with good yields (Table 2). The results in Table 2 demonstrate the broad scope of this TCRA methodology covering a structurally diverse group of CH-acids **2a−o** with many of the yields obtained being very good or, indeed, better than previously published four-step alkylation reactions.[2] The structure and regiochemistry of TCRA products **5aa−ao** were confirmed by NMR and mass analysis.

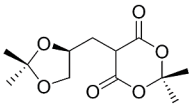
Chiral TCRA products **5aa−ac** are an important intermediates for the asymmetric synthesis of natural products like HIV-1 protease inhibitors **A-D**, phospholipase A_2 inhibitors **E-F**, antibiotic agglomerins **G**, (*R*)-γ-hexanolide **H** and (+)-brefeldin-A **I** as demonstrated in this paper,[1a−i] TCRA products **5ag−ak** could be an important intermediates for the synthesis of Wieland−Miescher (W−M) ketone and Hajos−Parrish (H−P) ketone analogues which are very good steroids drug intermediates,[3a,b] and TCRA product (−)-**5an** could serve as useful synthon for the synthesis of (−)-4,5-dihydroxy-D-threo-L-norvaline **J** and also for the synthesis of antibiotic clavalanine **K**, emphasizing the value of this cascade TCRA approach.

Diversity-Oriented Chiral Synthesis of TCRA Products 5ba−bk. With the optimized TCRA reaction conditions in hand, the scope of the L-proline-catalyzed cascade O/H reactions were investigated with different chiral α-amino aldehydes **1b−d**, various CH-acids **2a−k**, and Hantzsch ester **3** as shown in Table 3. A series of chiral α-amino aldehydes **1b−d** (1 equiv) reacted with Meldrum's acid **2a** and Hantzsch

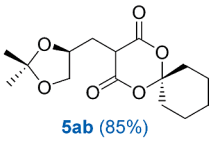
TABLE 2. Synthesis of Chiral Products 5aa−ao via Reductive Alkylation Reaction[a]



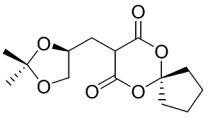
1a 2a-o 3, E = CO_2Et 5aa-ao



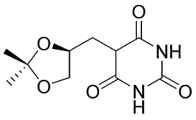
5aa (95%)
$[\alpha]^{25}_D$ = – 24.4 (*c* 1.0, $CHCl_3$)



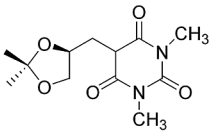
5ab (85%)
$[\alpha]^{25}_D$ = – 26.0 (*c* 1.0, $CHCl_3$)



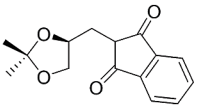
5ac (91%)
$[\alpha]^{25}_D$ = – 23.4 (*c* 1.0, $CHCl_3$)



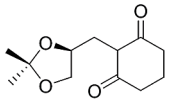
5ad (75%)
$[\alpha]^{25}_D$ = – 31.4 (*c* 0.45, EtOH)



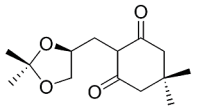
5ae (87%)
$[\alpha]^{25}_D$ = – 31.4 (*c* 1.0, $CHCl_3$)



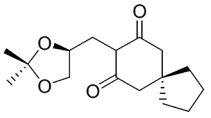
5af (98%)
$[\alpha]^{25}_D$ = – 41.5 (*c* 1.2, EtOH)



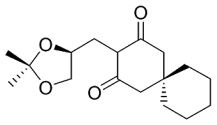
5ag (90%)[b]
$[\alpha]^{25}_D$ = – 41.0 (*c* 0.2, EtOH)



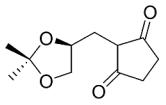
5ah (85%)
$[\alpha]^{25}_D$ = – 4.0 (*c* 1.0, EtOH)



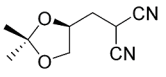
5ai (75%)
$[\alpha]^{25}_D$ = + 15.0 (*c* 0.4, EtOH)



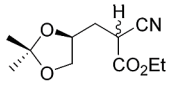
5aj (95%)
$[\alpha]^{25}_D$ = + 14.0 (*c* 0.5, EtOH)



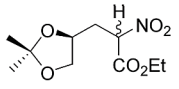
5ak (90%)[b]
$[\alpha]^{25}_D$ = – 32.1 (*c* 0.3, EtOH)



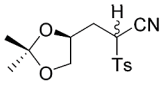
5al (99%)
$[\alpha]^{25}_D$ = – 46.7 (*c* 1.0, $CHCl_3$)



5am (70%; dr 1:1)
$[\alpha]^{25}_D$ = – 17.7 (*c* 1.0, EtOH)



5an (90%; dr 1:1)
$[\alpha]^{25}_D$ = – 10.5 (*c* 0.4, EtOH)



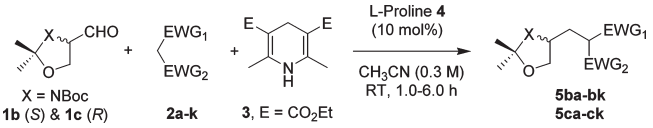
5ao (80%; dr 2:1)
$[\alpha]^{25}_D$ = – 26.2 (*c* 0.6, $CHCl_3$)

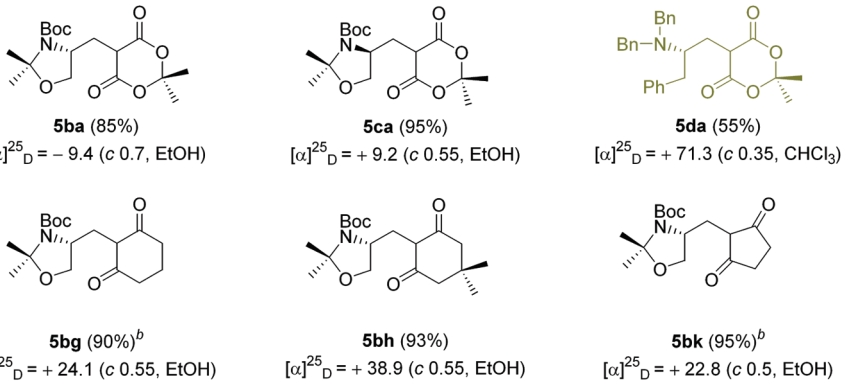
[a]Yield refers to the column purified product. [b](*R*)-Glyceraldehyde acetonide **1a** was taken as 3 equiv.

ester **3** catalyzed by 10 mol % of L-proline at 25 °C in CH_3CN (Table 3). The (*R*)-4-(2,2-dimethyl-4,6-dioxo[1,3]dioxan-5-ylmethyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester **5ba**, (*S*)-4-(2,2-dimethyl-4,6-dioxo[1,3]dioxan-5-ylmethyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester **5ca**, and (*R*)-5-(2-dibenzylamino-3-phenylpropyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **5da** were obtained in an enantiomerically pure manner with excellent to good yields. The reaction of (*S*)-Garner aldehyde **1b** with cyclohexane-1,3-dione **2g** and Hantzsch ester **3** under L-proline-catalysis furnished the TCRA product (*R*)-**5bg** as single enantiomer in 90% yield at 25 °C (Table 3). In a similar manner, reaction of (*S*)-Garner aldehyde **1b** with 5,5-dimethylcyclohexane-1,3-dione **2h**/cyclopentane-1,3-dione **2k** and Hantzsch ester **3** in CH_3CN at 25 °C for 1−6 h under L-proline-catalysis furnished the TCRA products (*R*)-**5bh** and (*R*)-**5bk** as single enantiomers in 93−95% yields, respectively (Table 3). The results in Table 3 demonstrate the broad scope of this reductive methodology covering a structurally diverse group of chiral α-amino aldehydes **1b−d** with many of the yields obtained being very good, or indeed better, than previously published four-step alkylation reactions.[2] The structure and regiochemistry of TCRA products **5ba−bk** were confirmed by NMR and mass analysis.

Applications of Chiral TCRA Products: (A) Development of Product-Specific MCC Reactions Based on the TCRA Platform. Chiral 2-alkylmalonates are an important class of compounds which are widely used as intermediates in the pharmaceutical and agrochemical industries.[1j−o] Compounds containing chiral 2-alkylmalonates have found pharmaceutical applications as glucocorticoid receptor modulators, peptide deformylase inhibitors, HIV-1 and HIV-2 protease inhibitors, potent dual ACE/NEP inhibitors, antidiabetic agents, ligands for the neuromodulatory receptor, and also starting materials for the synthesis of

TABLE 3. Synthesis of Chiral Products 5ba−bk via Reductive Alkylation Reaction[a]





[a]Yield refers to the column purified product. [b]Garner aldehyde **1b** was taken as 3 equivalents.

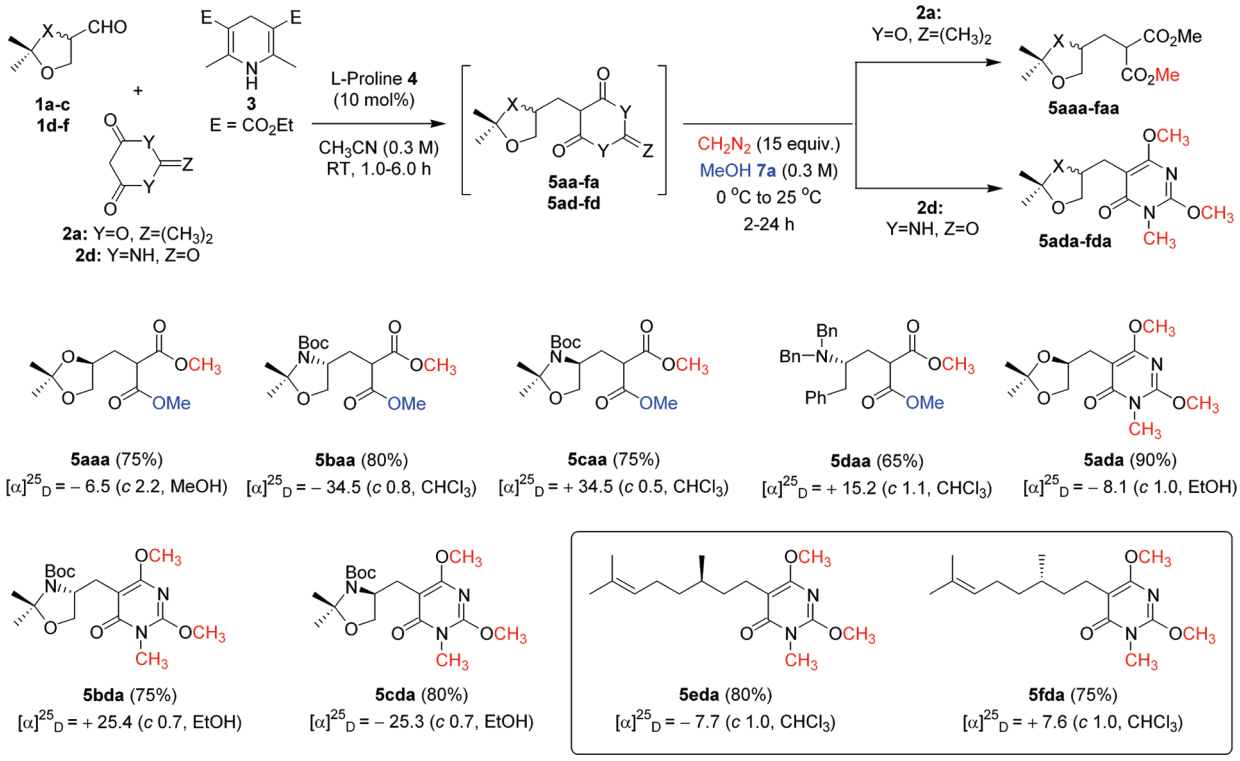
natural products as shown in Chart 1.[1] As such, the development of more general catalytic methods for their preparation is of significant interest.[2] The conventional method to synthesize chiral 2-alkylmalonates is the alkylation of dialkyl malonates with chiral alkyl halides under the dry reaction conditions, which has less scope with respect of yields, diverse library generation, and experimental simplicity (see eq 1).[2] Surprisingly, the amino acid-catalyzed cascade O/H reaction sequence could not work with dialkylmalonates **2p** as CH-acid; even the first step of the olefination itself did not take place. To overcome this reactivity problem, herein we discovered the synthesis of chiral 2-alkylmalonates in a sequential manner by utilization of reactive species of methoxycarbonylketenes to generate the library of chiral 2-alkylmalonates via in situ *O*-alkylation/ketenization/esterification (A/K/E) of TCRA product **5aa** with CH_2N_2 in one pot under ambient conditions, an approach we call "MCC approach to chiral 2-alkylmalonates" (Table 4).[3c]

L-Proline-catalyzed TCRA reaction of (*R*)-**1a** and Meldrum's acid **2a** with Hantzsch ester **3** in CH_3CN at 25 °C for 1 h furnished the expected TCRA product (*S*)-**5aa** in >99% conversion, which on in situ treatment with ethereal diazomethane in MeOH **7a** at 0 °C → 25 °C for 8 h furnished the expected (*S*)-dimethyl 2-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)malonate **5aaa** with 75% yield and >98% ee (based on HPLC analysis of **5aaa** derivative; see the Supporting Information for more information) through the *O*-alkylation/ketenization/esterification (A/K/E) sequence (Table 4, entry 1). The TCRA/A/K/E reaction of Meldrum's acid analogues **2b**,**c** with (*R*)-**1a**, **3**, **7a**, and diazomethane catalyzed by **4** in methanol at 0 °C → 25 °C for 24 h furnished the expected (*S*)-**5aaa** with 55−60% yields, >98% ee, respectively, and these results are not superior as compared to **2a** with respect to yields (results not shown in Table 4). After these interesting results, we decided to investigate the scope and limitations of the MCC reaction with other three chiral α-amino aldehydes **1b**−**d** with **2a**, **3**, **7a**, and diazomethane under L-proline-catalysis under ambient conditions (Table 4, entries 2−4). MCC reaction of chiral α-amino aldehydes (*S*)-**1b**, (*R*)-**1c**, and (*S*)-**1d** with **2a**, **3**, and **7a** and diazomethane under L-proline-catalysis furnished the expected enantiomerically pure products (−)-**5baa**, (+)-**5caa**, and (+)-**5daa** in 80−65% yields, respectively, as shown in Table 4, entries 2−4.

After these interesting results, we further decided to investigate the scope and limitations of the MCC reaction with a range of chiral aldehydes **1a**−**f**, barbituric acids **2d**, **3**, and **7a**, and diazomethane under L-proline-catalysis under ambient conditions to test the diverse nature of the MCC reaction (Table 4). As shown in Table 4, the MCC reaction of (*R*)-**1a**, barbituric acid **2d**, **3**, **7a** and diazomethane furnished the (*S*)-5-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-2,6-dimethoxy-3-methyl-3*H*-pyrimidin-4-one **5ada** as major single product with 90% yield out of 24 theoretically expected products from the designed reaction as shown in Table 4 and Table S1 (Supporting Information). (*S*)-5-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)pyrimidine-2,4,6-trione **5ad**, which is in situ generated from TCRA reaction, has many active sites toward methylation with diazomethane, but interestingly, we are able to obtain **5ada** as single major product, which is confirmed by NMR and UV spectral analysis. The generality of the product-specific MCC reaction was confirmed by four more examples with chiral aldehydes **1b**−**f**, **2d**, **3**, **7a**, and diazomethane under L-proline-catalysis and furnished the expected enantiomerically pure single MCC products **5bda**−**fda** with 75−80% yields, respectively, as shown in Table 4. Pyrimidinone derivatives **5ada**−**fda** are useful compounds as agrochemical fungicides and potent HIV-1 and HIV-2 inhibitors with good antiviral and antibacterial activity.[1j−o] This product-specific MCC technology may be suitable for development of a large number of diverse compounds of **5** to screen and identify the suitable bioactive products.

B. Brønsted Acid-Catalyzed Intramolecular Cyclization of Chiral TCRA Products. Functionalized chiral γ-butyrolactones

TABLE 4. Synthesis of Chiral Products 5aaa−fda via MCC Reaction[a]



[a]Yield refers to the column purified product.

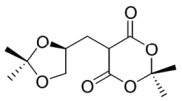
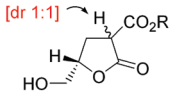
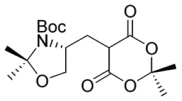
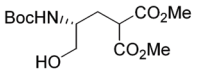
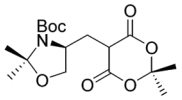
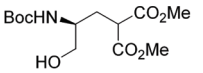
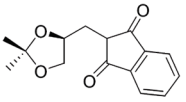
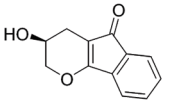
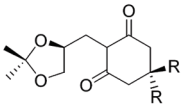
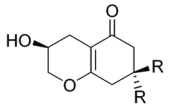
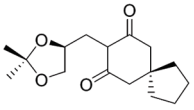
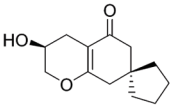
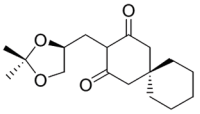
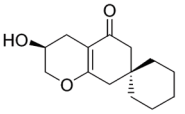
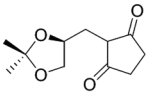
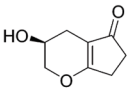
8 and protected γ-carboxy-L/D-glutamic acids **9** are very good intermediates for the synthesis of pharmaceutically useful natural and non-natural products as shown in Chart 1.[1] Surprisingly, to the best of our knowledge there is no report for the high-yielding asymmetric synthesis of useful chiral γ-butyrolactones **8** and higher analogues **10** through single step. Herein, we are presenting the asymmetric synthesis of **8**, **9**, and **10** with ≥98% ee and 80−99% yields via Brønsted acid-catalyzed cyclization of TCRA products **5** in protic or aprotic solvents as shown in Table 5. With an efficient amino acid-catalyzed reductive alkylation protocol in hand, we continued our investigation for the synthesis of functionalized chiral γ-butyrolactones **8** from (*S*)-5-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **5aa** under Brønsted acid-catalysis in MeOH/BnOH through cascade hydrolysis/lactonization/esterification (H/L/E) reactions as shown in Table 5, entry 1.

After complete investigation, we came to a conclusion that *p*-TSA is suitable Brønsted acid-catalyst for the H/L/E reactions compare to other Brønsted acid catalysts (results not shown in Table 5). Interestingly, reaction of (−)-**5aa** with 30 mol % of *p*-TSA in MeOH **7a** at 25 °C for 1−2 h furnished the chemoselectively single compound chiral γ-butyrolactone (+)-**8aaa** with 1:1 dr in 99% yield (Table 5, entry 1). Same H/L/E reaction under *p*-TSA-catalysis in BnOH **7b** at 25 °C for 1−2 h furnished the expected single chiral γ-butyrolactone product (+)-**8aab** with 1:1 dr in 99% yield (Table 5, entry 1). We envisioned that reaction of the (−)-**5aa** with *p*-TSA catalysis in protic solvents at 25 °C for 1−2 h furnished the chemoselectively H/L/E products (+)-**8aaa**−**aab** as single products in 99% yields instead of 5-hydroxy-2-oxo-tetrahydro-pyran-3-carboxylic acid alkyl esters, which is revealed by NMR analysis and also by DFT calculations (see the Supporting Information). The calculated heat of formation (ΔΔ*E*) for the (+)-**8aaa** product is 3.2 kcal/mol more than the six-membered ring formation reaction as shown in Table 5, entry 1. This result also strongly suggests that kinetically and thermodynamically γ-butyrolactone products (+)-**8aaa**−**aab** formation is more favorable than 5-hydroxy-2-oxotetrahydropyran-3-carboxylic acid alkyl esters formation as revealed by experimental and DFT calculations.

Brønsted acid-catalyzed cascade hydrolysis/esterification (H/E) reaction of (−)-**5ba** at 25 °C for 2 h in MeOH **7a** furnished the chemoselectively protected γ-carboxy-L-glutamic acid [L-Gla] (+)-**9baa** with 97% yield as a single compound (Table 5, entry 2). In a similar manner, reaction of (+)-**5ca** under *p*-TSA-catalysis at 25 °C for 2.5 h in MeOH **7a** furnished the protected D-Gla (−)-**9caa** with 95% yield as a single compound (Table 5, entry 3). Formation of **9baa**−**caa** as single products/isomers from a cascade H/E reaction could be explained on the basis of the relatively weak nucleophilic nature of in situ generated primary OH and NHBoc groups toward ester. H/E products of protected L-Gla and D-Gla **9baa**−**caa** are an important component of several vitamin K dependent blood clotting factors, including prothrobin, and also potentially useful building blocks in the total synthesis of quinocarcin and related bioactive natural products,[1p,q] which emphasizes the pioneering role of the cascade H/E approach.

With an efficient Brønsted acid-catalyzed H/L/E and H/E protocol in hand, we continued our investigation for the

TABLE 5. Brønsted Acid-Catalyzed Intramolecular Cyclization of Chiral TCRA Products 5[a]

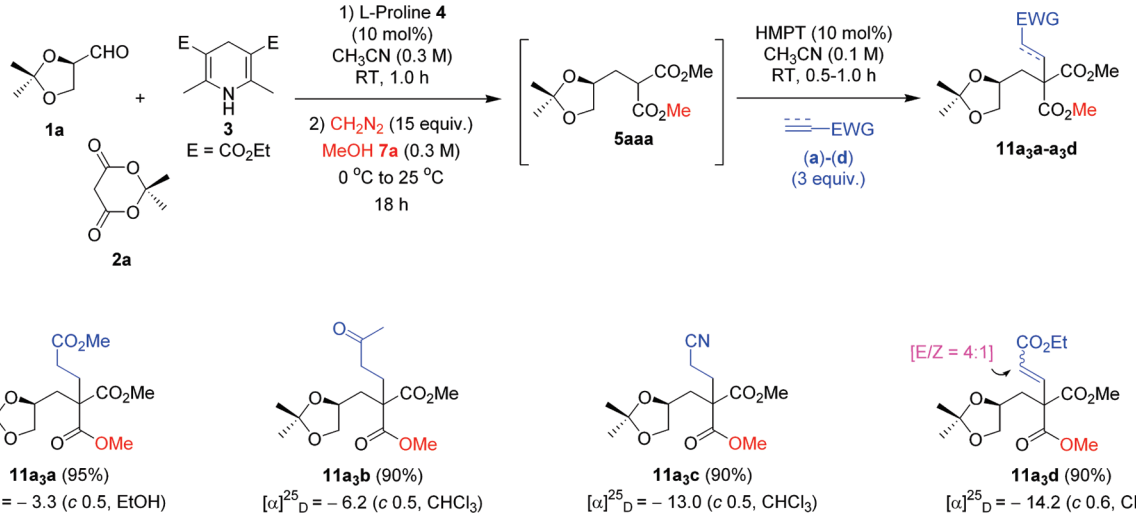
entry	substrate	conditions	product
1	 (–)-**5aa**	*p*-TSA (30 mol%) ROH **7a-b** (0.1 M) RT, 1-2 h	 [dr 1:1] R = Me: (+)-**8aaa** (99%) R = Bn: (+)-**8aab** (99%)
2	 (–)-**5ba**	*p*-TSA (30 mol%) MeOH **7a** (0.1 M) RT, 2 h	 (+)-**9baa** (97%)
3	 (+)-**5ca**	*p*-TSA (30 mol%) MeOH **7a** (0.1 M) RT, 2.5 h	 (–)-**9caa** (95%)
4	 (–)-**5af**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 2-3 h	 (–)-**10af** (88%)
5	 R = H: (–)-**5ag** R = Me: (–)-**5ah**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 3-5 h	 R = H: (–)-**10ag** (93%) R = Me: (–)-**10ah** (91%)
6	 (+)-**5ai**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 4-5 h	 (–)-**10ai** (91%)
7	 (+)-**5aj**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 1-2 h	 (–)-**10aj** (80%)
8	 (–)-**5ak**	*p*-TSA (30 mol%) CH_2Cl_2 (0.1 M) RT, 2-3 h	 (–)-**10ak** (90%)

[a]Yield refers to the column purified product.

synthesis of functionalized chiral 3-hydroxy-2,3,4,6,7,8-hexahydrochromen-5-ones **10af**−**ak** from chiral TCRA products **5af**−**ak** under Brønsted acid-catalysis through cascade hydrolysis/oxy-Michael/dehydration (H/OM/DH) reactions as shown in Table 5, entries 4−8. Interestingly, reaction of (−)-**5af** with 30 mol % of *p*-TSA in CH_2Cl_2 at 25 °C for 2−3 h furnished the chemoselectively single chiral product (−)-**10af** with 88% yield through H/OM/DH reactions (Table 5, entry 4). In a similar manner, reaction of (−)-**5ag** with 30 mol % of *p*-TSA in CH_2Cl_2 at 25 °C for 3−5 h furnished the chemoselectively single chiral product (−)-**10ag** with 93% yield through H/OM/DH reactions (Table 5, entry 5). The generality of the product-specific H/OM/DH reaction was confirmed by four more examples with chiral TCRA compounds **5ah**−**ak** under *p*-TSA-catalysis and furnished the expected enantiomerically pure single H/OM/DH products **10ah**−**ak** with 80−91% yields, respectively, as shown in Table 5, entries 5−8. Unexpected chemoselectivity of H/OM/DH reactions could be explained on the basis of the more nucleophilic nature of in situ generated primary OH group than secondary OH in the oxy-Michael step.

(6) (a) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059–3077. (b) Atwal, K. S.; Wang, P.; Rogers, W. L.; Sleph, P.; Monshizadegan, H.; Ferrara, F. N.; Traeger, S.; Green, D. W.; Grover, G. J. *J. Med. Chem.* **2004**, *47*, 1081–1084. (c) Frédérick, R.; Robert, S.; Charlier, C.; Ruyck, J.; Wouters, J.; Pirotte, B.; Masereel, B.; Pochet, L. *J. Med. Chem.* **2005**, *48*, 7592–7603. (d) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481–4484. (e) Ross, S. A.; Sultana, G. N. N.; Burandt, C. L.; ElSohly, M. A.; Marais, J. P. J.; Ferreira, D. *J. Nat. Prod.* **2004**, *67*, 88–90. (f) Burlison, J. A.; Neckers, L.; Smith, A. B.; Maxwell, A.; Blagg, B. S. J. *J. Am. Chem. Soc.* **2006**, *128*, 15529–15536. (g) Shi, Y.-L.; Shi, M. *Org. Biomol. Chem.* **2007**, *5*, 1499–1504. (h) Wijeratne, E. M. K.; Turbyville, T. J.; Fritz, A.; Whitesell, L.; Gunatilaka, A. A. L. *Bioorg. Med. Chem.* **2006**, *14*, 7917–7923. (i) Rezanka, T.; Sigler, K. *J. Nat. Prod.* **2007**, *70*, 1487–1491. (j) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953.

TABLE 6. Synthesis of Chiral Products 11 with Quaternary Carbons via MCC Reaction[a]



[a]Yield refers to the column purified product.

Functionalized chromanes and chromenes are of considerable importance in a variety of industries. These heterocyclic analogues **10af**−**ak** are widespread elements in natural products and have attracted much attention from a wide area of science, including physical chemistry, medicinal chemistry, natural product chemistry, synthetic organic chemistry, and polymer science.[6] As such, the development of more general catalytic asymmetric methods for their preparation is of significant interest and our presently developed cascade chemistry will be useful to develop library of chiral chromanes and chromenes in very good yields with high selectivity.

C. Sequential Cascade Synthesis of Asymmetric Compounds with Quaternary Carbons through MCC Reactions Based on TCRA Platform. Stereoselective synthesis of highly functionalized chiral compounds with quaternary carbons are evergreen task in synthetic organic chemistry.[7] As part of our research program to engineer direct MCC reactions in sequential manner to deliver the highly functionalized chiral molecules with quaternary carbons and also on the demand of pharmaceutical applications, we extended the five-component TCRA/A/K/E reactions into L-proline-HMPT-catalyzed six-component TCRA/A/K/E/A reaction of (*R*)-glyceraldehyde acetonide **1a**, Meldrum's acid **2a**, Hantzsch ester **3**, diazomethane, and methanol **7a** with various active olefins and acetylenes (**a**−**d**) in one pot (Table 6). MCC products **11** were constructed in very good yields with high selectivity, and this method will have a great impact on the synthesis of functionalized small chiral molecules with a quaternary carbon as shown in Table 6. Highly substituted asymmetric 2,2-dialkylated malonates **11** have gained importance in recent years as starting materials and intermediates for the synthesis of biologically active compounds, for example, M_2-selective muscarinic receptor antagonists and isozyme-selective glutathione *S*-transferase inhibitors.[1j−o]

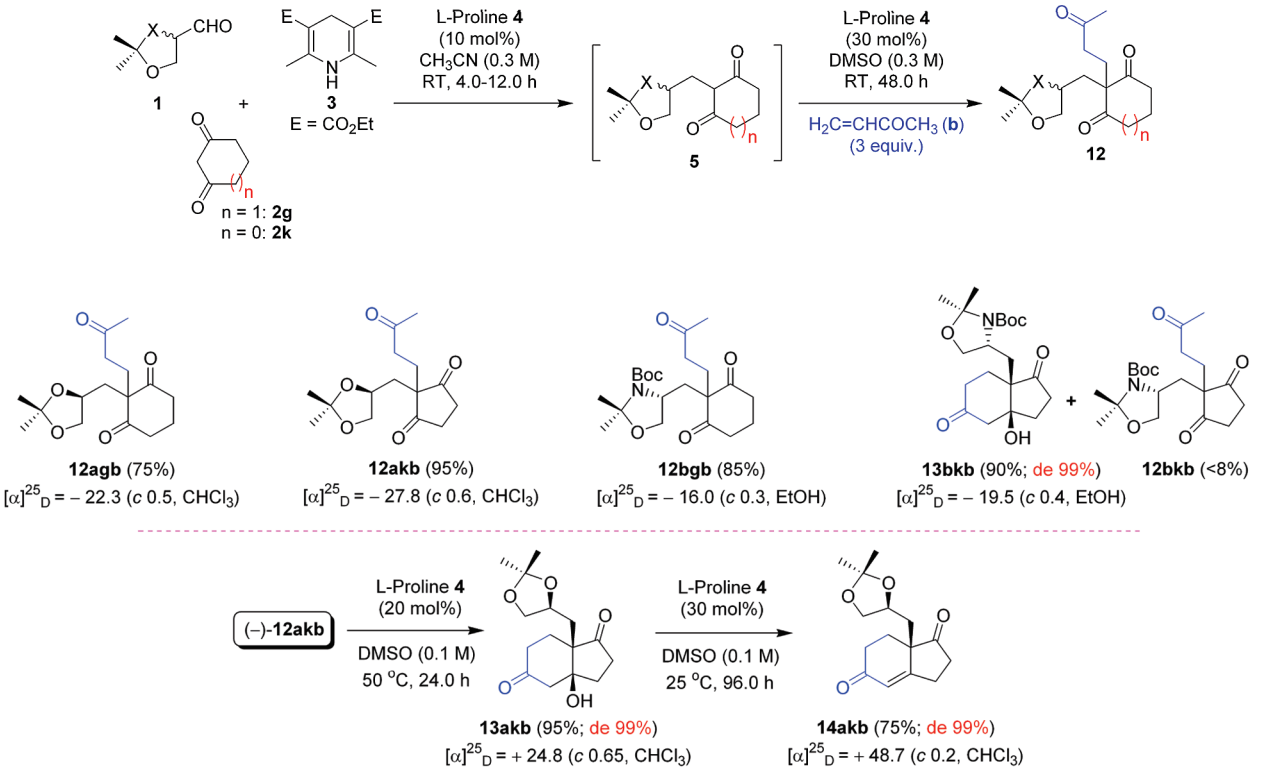
The TCRA reaction of (*R*)-**1a**, **2a**, and **3** under 10 mol % of L-proline-catalysis furnished the compound (−)-**5aa** with >99% conversion, which on in situ treatment with ethereal diazomethane at 0−25 °C for 8 h furnished the chemoselective TCRA/A/K/E product (−)-**5aaa** with >99% conversion, which on in situ treatment with methyl acrylate (**a**) under 10 mol % of hexamethylphosphorous triamide (HMPT) catalysis in CH_3CN at 25 °C for 0.5−1.0 h furnished the TCRA/A/K/E/A product (−)-**11a$_3$a** with 95% yield as shown in Table 6.[8] The generality of the L-proline-HMPT-catalyzed chemoselective sequential one-pot TCRA/A/K/E/A reaction is further confirmed by three more examples using methyl vinyl ketone (**b**), acrylonitrile (**c**), and methyl propiolate (**d**) to furnish the expected (−)-**11a$_3$b** in 90% yield, (−)-**11a$_3$c** in 90% yield, and (−)-**11a$_3$d** in 90% yield with >60% de, respectively, as shown in Table 6. For the pharmaceutical applications, diversity-oriented library of chiral malonates **11** could be generated by using this MCC technology.

D. Sequential Cascade Asymmetric Synthesis of Hajos−Parrish Ketone Analogues through MCC Reactions Based on the TCRA Platform. Higher alkyl-substituted chiral Wieland−Miescher (W−M) and Hajos−Parrish (H−P) ketone analogues **13/14** are good intermediates for the synthesis of natural products like steroids, and also higher alkyl W−M and H−P ketone analogues **13/14** are very good intermediates for the synthesis of pharmaceutically acceptable salts or hydrates of heterocycles, which are shown as selective glucocorticoid receptor modulators for treating a variety of autoimmune and inflammatory diseases.[9] Interestingly, to the best of our knowledge, there is no report for the asymmetric synthesis of useful higher alkyl substituted H−P ketone analogues **13/14**. In this paper, we are

(7) For the selected reviews on quaternary carbon generation, see: (a) Austeri, M.; Buron, F.; Constant, S.; Lacour, J.; Linder, D.; Muller, J.; Tortoioli, S. *Pure Appl. Chem.* **2008**, *80*, 967–977. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. (d) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146. (e) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597. (f) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. (g) Srikrishna, A.; Krishnan, K.; Nagaraju, S. *J. Indian Inst. Sci.* **1994**, *74*, 157–168. (h) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569.

(8) For HMPT-catalyzed Michael reactions, see: Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871–874.

TABLE 7. Asymmetric Synthesis of H−P Ketone Analogues 13 and 14 via MCC Reaction[a]



[a]Yield refers to the column purified product.

presenting the asymmetric synthesis of H−P ketone analogues **13/14** with very good ee/de and yields through MCC reactions based on TCRA platform as shown in Table 7.

We were surprised to know that L-proline-catalyzed TCRA reaction of 3 equiv of (*R*)-glyceraldehyde acetonide **1a** with cyclohexane-1,3-dione **2g** and Hantzsch ester **3** in

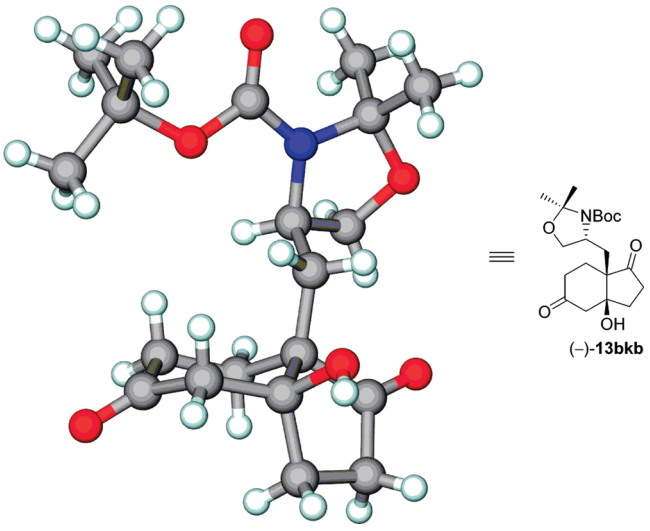
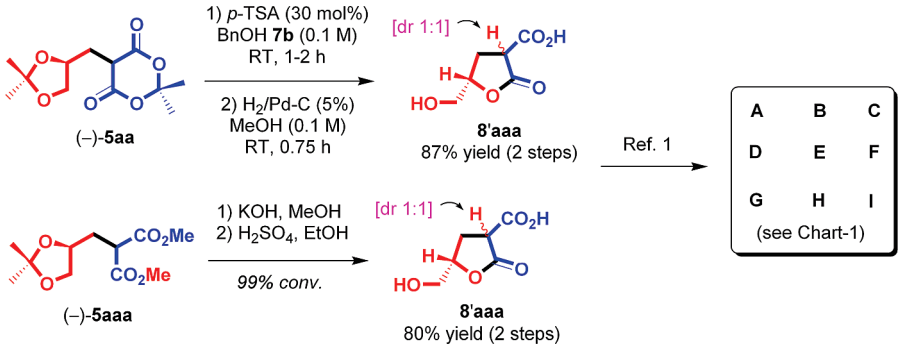


FIGURE 1. Crystal structure of 4-(7a-hydroxy-3,6-dioxooctahydroinden-3a-ylmethyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (**13bkb**).

CH_3CN at 25 °C for 5.0 h furnished the expected TCRA product (−)-**5ag** with good conversion, which on further removing the solvent CH_3CN by vacuum pump, adding solvent DMSO, 30 mol % of L-proline **4**, and 3 equiv of methyl vinyl ketone (**b**) to the reaction mixture, and stirring at 25 °C for 2 days furnished the only Michael adduct (−)-**12agb** with 75% yield and >98% ee instead of the expected

(9) Applications of Wieland−Miescher (W−M) ketone analogues; see: (a) Paquette, L. A.; Wang, H.-L. *J. Org. Chem.* **1996**, *61*, 5352–5357. (b) Deng, W.; Jensen, M. S.; Overman, L. E.; Rucker, P. V.; Vionnet, J.-P. *J. Org. Chem.* **1996**, *61*, 6760–6761. (c) Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terashima, S. *Org. Lett.* **2001**, *3*, 2701–2704. (d) Inomata, K.; Barrague, M.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 533–539. (e) Nagamine, T.; Inomata, K.; Endo, Y.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 123–131. Applications of Hajos−Parrish (H−P) ketone analogues; see: (f) Majetich, G.; Song, J. S.; Ringold, C.; Nemeth, G. A.; Newton, M. G. *J. Org. Chem.* **1991**, *56*, 3973–3988. (g) Ruprah, P. K.; Cros, J. −P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2002**, 3145–3152. (h) Cao, L.; Sun, J.; Wang, X.; Zhu, R.; Shi, H.; Hu, Y. *Tetrahedron* **2007**, *63*, 5036–5041. (i) Kasch, H.; Liedtke, B.; *U. S. Pat. Appl. Publ.* **2006**, 24 pp, CODEN: USXXCO US 2006089340 A1 20060427, CAN 144:433022 (patent written in English). (j) Sevillano, L. G.; Melero, C. P.; Boya, M.; Lopez, J. L.; Tome, F.; Caballero, E.; Carron, R.; Montero, M. J.; Medarde, M.; San Feliciano, A. *Bioorg. Med. Chem.* **1999**, *7*, 2991–3001. For the pharmaceutical applications of W−M and H−P ketone analogues, see: (k) Thompson, C. F.; Quraishi, N.; Ali, A.; Mosley, R. T.; Tata, J. R.; Hammond, M. L.; Balkovec, J. M.; Einstein, M.; Ge, L.; Harris, G.; Kelly, T. M.; Mazur, P.; Pandit, S.; Santoro, J.; Sitlani, A.; Wang, C.; Williamson, J.; Miller, D. K.; Yamin, T. D.; Thompson, C. M.; O'Neill, E. A.; Zaller, D.; Forrest, M. J.; Carballo-Jane, E.; Luell, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3354–3361. (l) Smith, C. J.; Ali, A.; Balkovec, J. M.; Graham, D. W.; Hammond, M. L.; Patel, G. F.; Rouen, G. P.; Smith, S. K.; Tata, J. R.; Einstein, M.; Ge, L.; Harris, G. S.; Kelly, T. M.; Mazur, P.; Thompson, C. M.; Wang, C. F.; Williamson, J. M.; Miller, D. K.; Pandit, S.; Santoro, J. C.; Sitlani, A.; Yamin, T. D.; O'Neill, E. A.; Zaller, D. M.; Carballo-Jane, E.; Forrest, M. J.; Luell, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2926–2931. (m) Ali, A.; Balkovec, J. M.; Beresis, R.; Colletti, S. L.; Graham, D. W.; Patel, G. F.; Smith, C. J. *PCT Int. Appl.* **2004**, CODEN: PIXXD2 WO 2004093805 A2 20041104, CAN 141:395547, (in English; 201 pp).

SCHEME 2. High-Yielding Synthesis of Chiral Building Block 8′aaa: Formal Synthesis of Natural Products (A−I)



W−M ketone analogue **13agb** as shown in Table 7. In a similar manner, L-proline-catalyzed TCRA reaction of 3 equiv of (*R*)-**1a** with cyclopentane-1,3-dione **2k** and Hantzsch ester **3** in CH_3CN at 25 °C for 3.0 h furnished the expected TCRA product (−)-**5ak** with good conversion, which on further removing the solvent CH_3CN by vacuum pump and adding solvent DMSO, 30 mol % of L-proline **4** and 3 equiv of methyl vinyl ketone (**b**) to the reaction mixture and stirring at 25 °C for 2 days furnished only the Michael adduct (−)-**12akb** with 95% yield and >98% ee instead of expected H−P ketone analogue **13akb** as shown in Table 7. Interestingly, treatment of (−)-**12akb** with 20 mol % of L-proline **4**-catalysis in DMSO at 50 °C for 24.0 h furnished the expected bicyclic alcohol (+)-**13akb** in 95% yield with >98% ee and 99% de. Hydrolysis of bicyclic alcohol (+)-**13akb** obtained from L-proline-catalysis with L-proline (30 mol %) in DMSO at 25 °C for 96 h furnished the expected bicyclic H−P ketone analogue (+)-**14akb** in good yield with >98% ee and 99% de as shown in Table 7.

With an efficient organocatalytic asymmetric sequential cascade Robinson annulation (RA) protocol in hand, the scope of the L-proline-L-proline-catalyzed sequential asymmetric RA reactions was investigated with Garner aldehyde (*S*)-**1b**. A series of cyclohexane-1,3-dione **2g**/cyclopentane-1,3-diones **2k** were reacted with 3.0 equiv of Garner aldehyde (*S*)-**1b** and Hantzsch ester **3** under 10 mol % of L-proline at 25 °C in CH_3CN for 4−5 h followed by treatment with 3.0 equiv of methyl vinyl ketone (**b**) catalyzed by 30 mol % of L-proline at 25 °C in DMSO for 48 h (Table 7). In the case of **2g**, the expected Michael adduct (−)-**12bgb** was only obtained in good yields with >98% ee as shown in Table 7. But interestingly, sequential RA reaction with **2k** furnished the bicyclic alcohol (−)-**13bkb** in 90% yield with >98% ee and 99% de along with Michael adduct **12bkb** as byproduct in <8% yield. The absolute configuration of product (−)-**13bkb** prepared under L-proline-L-proline-catalysis was established by using X-ray crystallography and also by comparison with the L-proline-catalyzed Hajos−Parrish−Eder−Sauer−Wiechert reaction.[10] The X-ray crystal structure of product (−)-**13bkb** is depicted in Figure 1.[11]

E. High-Yielding Synthesis of Chiral Building Blocks for Natural Products Synthesis: Formal Total Synthesis of HIV-1 Protease Inhibitors, Phospholipase A_2 Inhibitors, Antibiotic Agglomerins, Brefeldin A, and (*R*)-γ-Hexanolide. After successful demonstration of the L-proline-catalyzed asymmetric TCRA reactions followed by development of MCC reactions with the combination of A/K/E, A/K/E/A, H/L/E, H/E, H/OM/DH, and RA reactions, we further decided to synthesize the chiral building blocks for natural products synthesis from MCC reactions as shown in Scheme 2. The design and implementation of MCC reactions is a challenging task of organic chemistry, yet one that can impart striking novelty, elegance, and efficiency to synthetic strategies. The application of MCC reactions to natural products synthesis represents a particularly demanding task, but the results can be both stunning and instructive. Herein, we highlight the design and execution of the combination of MCC reactions for the high-yielding synthesis of key intermediates in the total synthesis with minimum synthetic steps as demonstrated with selected natural product examples.[12]

Recently, chiral (5*S*)-5-hydroxymethyl-2-oxotetrahydrofuran-3-carboxylic acid **8′aaa** was used as a key intermediate for the total synthesis of HIV-1 protease inhibitors **A**−**D**, phospholipase A_2 inhibitors **E** and **F**, antibiotic agglomerins **G**, (*R*)-γ-hexanolide **H**, and (+)-brefeldin A **I** as shown in Scheme 2.[1a−i] Ohta et al. and Kitahara et al. prepared the key intermediate **8′aaa** in six steps starting from (*R*)-glyceraldehyde acetonide **1a** with an overall yield of 40% in their total synthesis of **A**−**F** and **I**, respectively.[1a−i] Herein, by the combination of cascade TCRA and H/L/E reactions, we prepared the key intermediate of chiral acid (5*S*)-**8′aaa** by using only three synthetic steps [TCRA, H/L/E, and hydrogenation] with overall yield of 83% with >98% ee as shown in Scheme 2. We also developed the other alternative method to prepare (5*S*)-**8′aaa** with overall yield of 60% with >98% ee by using again three synthetic steps [TCRA/A/K/E, hydrolysis (H) and lactonization (L)], which is similar to the previous approach for cyclization as shown in Scheme 2. Herein, we have demonstrated the successful combination of two cascades TCRA and H/L/E with hydrogenation; or/and

(10) (a) Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas, C. F. III. *J. Am. Chem. Soc.* **1997**, *119*, 8131–8132. (b) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283. (c) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912. (d) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16–17. (e) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479. (f) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839–5842. (g) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569.

(11) CCDC-743987 for (−)-**13bkb** contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or mail to: deposit@ccdc.cam.ac.uk.

(12) For the total synthesis of natural products through cascade reactions, see: Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009. and references cited therein.

TCRA/A/K/E with hydrolysis (H)/lactonization (L) to furnish the (5*S*)-**8′aaa** with overall yield of >83% with >98% ee, which is utilized as key chiral building block for the total synthesis of natural products **A**−**I** as shown in Scheme 2.

Conclusions

In summary, we have developed the metal-free and MCC process for the asymmetric synthesis of highly substituted chiral building blocks (2-alkyl-CH-acids, 2-alkylcyclohexane-1,3-diones, 2-alkylcyclopentane-1,3-diones, and H−P ketone analogues) based on the three-component reductive alkylation's (TCRA) platform. We developed the single-step alkylation of variety of CH-acids with (*R*)-glyceraldehyde acetonide/(*S*)-Garner aldehyde and Hantzsch ester through amino acid-catalyzed TCRA reaction without racemization in very good yields. Direct combination of L-proline-catalyzed TCRA reaction with other reactions like alkylation/ketenization/esterification (A/K/E), alkylation/ketenization/esterification/alkylation (A/K/E/A), hydrolysis/lactonization/esterification (H/L/E), hydrolysis/esterification (H/E), hydrolysis/oxy-Michael/dehydration (H/OM/DH), and Robinson annulation (RA) of CH-acids, chiral aldehydes, Hantzsch ester, diazomethane, and methyl vinyl ketone furnished the highly functionalized chiral building blocks with good to high yields and with excellent diastereoselectivities. Many of the chiral building blocks [**5aa**, **5ba**, **5ca**, **5ag**, **5ak**, **5bg**, **5bk**, **5am**, **5an**, **5aaa**, **8aab**, **9baa**, and **9caa**] prepared via MCC reactions are illustrated direct application in pharmaceutical chemistry. Further work is in progress to utilize TCRA reactions in synthetic chemistry.

Experimental Section

General Experimental Procedures for the MCC Reactions. L-Proline-Catalyzed Cascade TCRA Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the chiral aldehyde **1**, 0.3 mmol of CH-acid **2a**−**o**, and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of solvent followed by the catalyst amino acid **4** (0.03 mmol, 10-mol %), and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1−3. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure TCRA products **5** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

L-Proline-Catalyzed Sequential TCRA/A/K/E Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the chiral aldehyde **1**, 0.3 mmol of Meldrum's acid **2a** or barbituric acid **2d**, and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of solvent followed by the catalyst amino acid **4** (0.03 mmol, 10 mol %), and the reaction mixture was stirred at 25 °C for the time indicated in Table 4. To the crude reaction mixture added 15 equiv of an ethereal solution of diazomethane followed by methanol **7a** (1.0 mL), and the reaction mixture was stirred at room temperature for the time indicated in Table 4. After evaporation of the solvent and excess diazomethane completely in fume hood, the crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure one-pot MCC products **5** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Brønsted Acid-Catalyzed Cascade H/L/E and H/OM/DH Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.1 mmol of the chiral TCRA product **5aa**−**ak** was added 1.0 mL of solvent followed by the catalyst *p*-TSA (0.03 mmol, 30 mol %), and the reaction mixture was stirred at 25 °C for the time indicated in Table 5. The crude reaction mixture washed with water, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure cascade H/L/E and H/OM/DH products **8**−**10** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

L-Proline-HMPT-Catalyzed Sequential TCRA/A/K/E/A Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the chiral aldehyde **1**, 0.3 mmol of Meldrum's acid **2a**, and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of CH_3CN followed by the catalyst amino acid **4** (0.03 mmol, 10 mol %), and the reaction mixture was stirred at 25 °C for the time indicated in Table 6. To the crude reaction mixture was added 15 equiv of an ethereal solution of diazomethane followed by methanol **7a** (1.0 mL), and the reaction mixture was stirred at room temperature for the time indicated in Table 6. After evaporation of the solvent and excess diazomethane completely in a fume hood, to the crude reaction mixture were added 3 equiv of active olefins/acetylenes (**a**−**d**), hexamethylphosphorous triamide (HMPT, 10 mol %), and CH_3CN (1.0 mL) and the mixture stirred at 25 °C for 0.5 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure one-pot chiral MCC products **11** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

L-Proline-L-Proline-Catalyzed Sequential Double-Cascade TCRA/Robinson Annulation Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **1**, 0.3 mmol of CH-acids **2 g/k**, and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of CH_3CN followed by the catalyst amino acid **4** (0.03 mmol), and the reaction mixture was stirred at 25 °C for the time indicated in Table 7. After evaporation of the solvent completely, to the crude reaction mixture were added 0.9 mmol of methyl vinyl ketone (**b**), 1.0 mL of DMSO solvent, and 0.09 mmol of L-proline **4a**, and the reaction mixture was stirred at 25 °C for 2 days. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure one-pot MCC products **12**−**14** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Acknowledgment. This work was made possible by a grant from the Department of Science and Technology (DST), New Delhi (Grant No. DST/SR/S1/OC-65/2008). Y.V.R. thanks Council of Scientific and Industrial Research (CSIR), New Delhi for a senior research fellowship. We thank Dr. P. Raghavaiah for his help in X-ray structural analysis.

Supporting Information Available: Complete experimental procedures, compound characterization, X-ray crystal structures, and analytical data (^1H NMR, ^{13}C NMR, HRMS, and elemental analysis) for all new compounds. Copies of ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.