Direct catalytic asymmetric synthesis of highly functionalized tetronic acids/tetrahydro-isobenzofuran-1,5-diones *via* combination of cascade three-component reductive alkylations and Michael-aldol reactions†

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Received 26th February 2010, Accepted 7th April 2010
First published as an Advance Article on the web 7th May 2010
DOI: 10.1039/c003588b

A practical and sustainable chemical process for the synthesis of highly substituted tetrahydro-isobenzofuran-1,5-diones was achieved for the first time through asymmetric cascade Michael-aldol reaction of 4-hydroxy-3-alkyl-5*H*-furan-2-ones with alkyl vinyl ketones in the presence of a catalytic amount of L-proline or 9-amino-9-deoxyepiquinine/TCA. In this article, we discovered for the first time the asymmetric synthesis of privileged bicyclic lactones through kinetic resolution and show the synthetic application to pharmaceuticals and natural products synthesis.

Introduction

Functionalized tetronic acids, 5,6-dihydro-pyran-2-ones, 4-hydroxy-chromen-2-ones and tetrahydro-isobenzofuran-1,5-diones are an important class of heterocycles, which display very large spectrum of biological activities and are widely used as synthetic intermediates, drug intermediates/ingredients in natural product synthesis and also in pharmaceuticals (see Chart 1).[1] As such, the development of new and more general catalytic asymmetric methods for their preparation is of significant interest.[2] Interestingly, to the best of our knowledge there is no report on the direct catalytic asymmetric method for the synthesis of functionalized tetrahydro-isobenzofuran-1,5-diones, which can serve as good intermediates for the total synthesis of natural and non-natural products as demonstrated in this work. Herein, first time we reported the organocatalytic cascade approach to the asymmetric synthesis of functionalized tetrahydro-isobenzofuran-1,5-diones *via* "sequential combination of cascade three-component reductive alkylation (TCRA) and Michael-aldol (M-A) reactions".[3]

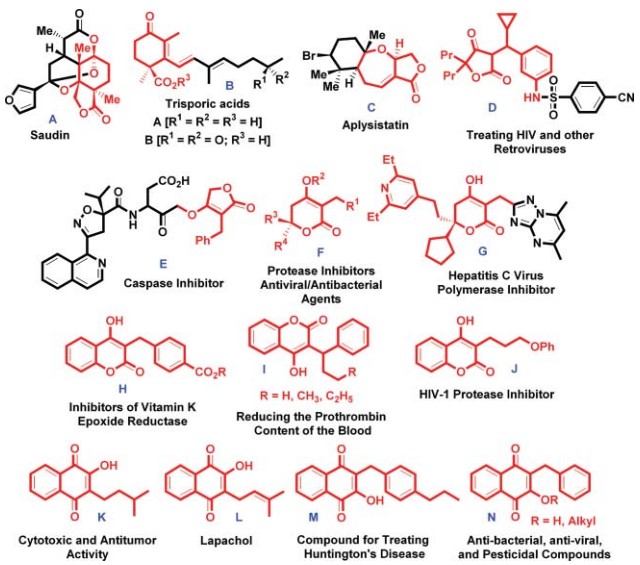
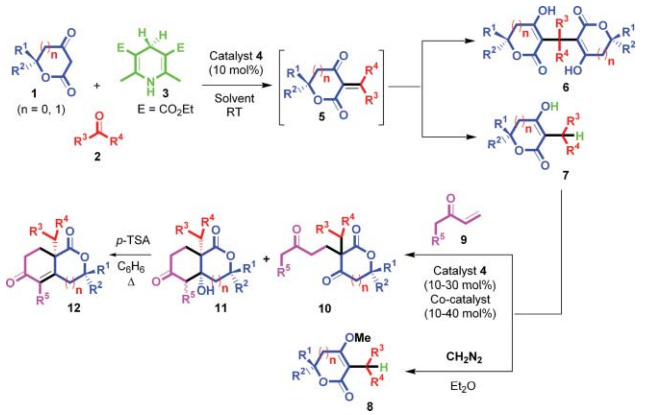


Chart 1 Natural and non-natural products library containing cascade TCRA and M-A compounds.

Recently Barbas, List and co-workers rediscovered the novel technology of amino acid-catalyzed intra-/inter-molecular aldol reactions of ketones/aldehydes with variety of carbonyls to provide a general route to a variety of aldol products in good yields with high enantioselectivity, which is known as Barbas-List aldol (BLA) reaction.[4] The advent of amino acid-catalyzed aldol reaction technology providing a high inspiration to scientific community to develop cellular type cascade reactions based on the *in situ* generated enamine/iminium chemistry.[4]

However, the amino acid-catalyzed intramolecular aldol reaction of diketo-lactones **10** is not known and resulting aldol products **11** and **12** are having a wide range of applications in natural products and pharmaceutical chemistry (see Chart 1 and Scheme 1) and also there is no direct asymmetric methodology available to prepare them by using the classical reaction strategies. Herein, we have reported a metal-free and novel technology



Scheme 1 Direct asymmetric cascade TCRA and M-A reactions.

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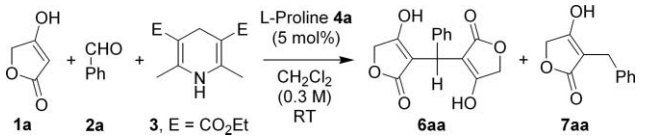
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. See DOI: 10.1039/c003588b

Table 1 Optimization for the cascade TCRA reaction of **1a**, **2a** and **3**[a]



1a 2a 3, E = CO_2Et 6aa 7aa

Entry	Aldehyde **2a** (equiv.)	H. ester **3** (equiv.)	Time/h	Products yield (%)[b] **6aa**	**7aa**
1	2.0	—	24	75	—
2	1.0	1.0	24	—	80
3	**2.0**	**1.0**	**5**	—	**90**
4	3.0	1.0	2	—	90

[a] Reactions were carried out in solvent (0.3 M) with 1–3 equiv. of **2a** relative to the **1a** and **3** (0.5 mmol) in the presence of 5-mol% of catalyst **4a**. [b] Yield refers to the column-purified product.

for the asymmetric synthesis of highly substituted tetrahydro-isobenzofuran-1,5-diones **11**/**12** by using the two-step sequential combination of organocatalytic cascade TCRA and M-A reactions from commercially available cyclic β-keto-lactones **1**, aldehydes/ketones **2**, organic hydride **3**, amines/amino acid **4** and alkyl vinyl ketones **9** (Scheme 1).

Over the last few years, we have been interested in an amino acid-catalyzed cascade TCRA reactions of CH-acids, aldehydes/ketones and organic hydride for the generation of reductive alkylation products *via* 1 x C–C/2 x C–H bonds formation in one-pot.[5] During our investigation for new reactive species for such TCRA processes and also for synthetic applications, we decided to explore the potential ability of the cyclic β-keto-lactones **1** as CH-acids to participate in an amino acid-catalyzed TCRA reaction with aldehydes/ketones **2** and organic hydride **3** (see Scheme 1). Herein, we report our findings regarding these new TCRA reactions and their synthetic applications.

Results and discussion

Amino acid-catalyzed TCRA reaction with tetronic acid: reaction optimization

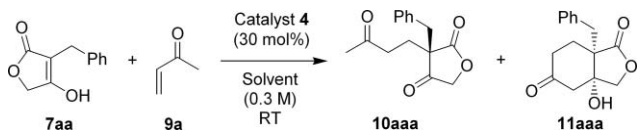
We observed that the reaction of tetronic acid **1a** with *in situ* generated iminium ion from benzaldehyde **2a** under proline-catalysis would lead to bis-adduct **6aa** in 75% yield without olefin **5aa** formation (Table 1, entry 1). However, when we used one equiv. of organic hydride **3** in cascade TCRA reaction of **1a** and **2a**, bis-adduct **6aa** were not detected and instead expected product **7aa** were obtained with 80% yield under the standard reaction conditions (Table 1, entry 2). The optimum conditions involved the use of 5-mol% catalyst **4a** and two equiv. of benzaldehyde **2a** in cascade TCRA reaction of **1a**, **2a** and **3** in CH_2Cl_2 at 25 °C for 5 h to furnish **7aa** in very good yield (Table 1, entry 3). TCRA product **7aa** is important intermediate for the total synthesis of caspase inhibitor (**E**) and which is emphasizing the value of this TCRA approach to the pharmaceuticals.[1h] This interesting result represents a novel methodology for the preparation of 3-alkyl-tetronic acids **7** and a new reactivity for amino acid catalysis.

Asymmetric cascade M-A reaction with 3-benzyl-tetronic acid: reaction optimization

After successful synthesis of 3-benzyl-tetronic acid **7aa**, we initiated our preliminary studies of the asymmetric cascade M-A reactions by screening a number of known and novel organocatalysts for the Michael-aldolization of **7aa** with 3 equiv. of methyl vinyl ketone **9a** and some representative results are shown in Table 2. Interestingly, cascade M-A reaction of **7aa** with 3 equiv. of methyl vinyl ketone **9a** in DMSO under 30-mol% of L-proline **4a**-catalysis furnished the Michael product (+)-**10aaa** in 10% yield with only 23% ee and cascade M-A product (–)-**11aaa** in 70% yield with 52% ee, which is enriched to 86% ee with 60–70% yield after one quick crystallization from isopropanol at 25 °C (Table 2, entry 1). Same reaction in DMSO under 30-mol% of D-proline **4b**-catalysis furnished the opposite enantiomer of Michael product (–)-**10aaa** in 10% yield with only 21% ee and cascade M-A product (+)-**11aaa** in 50% yield with 53% ee, which is enriched to 92% ee with 60–70% yield after one quick crystallization from isopropanol at 25 °C (Table 2, entry 2).

To further improvement of ee/yield of cascade products **10aaa**/**11aaa**, we also tested number of primary-/secondary-amino acids, chiral pyrrolidines and *tert*-amines based on cinchona alkaloids like L-phenylalanine **4c**, L-tryptophan **4d**, O^{t}Bu-L-threonine **4e**, D-amino-phenyl-acetic acid **4f**, 4-benzyl-1-methyl-imidazolidine-2-carboxylic acid **4g**, L-DPP **4h**, L-DPPOTMS **4i**, D-DPPOTMS **4j**, L-(3,5-Me_2)$_2$DPPOTMS **4k**,

Table 2 Optimization for the cascade M-A reaction of **7aa** and **9a**[a]



7aa 9a 10aaa 11aaa

Entry	Catalyst **4** (30 mol%)	Solvent (0.3 M)	Time/h	Products yield (%)[b] **10aaa**	**11aaa**	Products ee (%)[c] **10aaa**	**11aaa**
1	L-proline **4a**	DMSO	48	10	70	–23	–52(–86)
2	D-proline **4b**	DMSO	48	10	50	21	53(92)
3[d]	**Q-NH_2/TCA 4u**	**THF**	**8**	**60**	**40**	**8**	**55(92)**

[a] Reactions were carried out in solvent (0.3 M) with 3 equiv. of **9a** relative to the **7aa** (0.5 mmol) in the presence of 30-mol% of catalyst **4**. [b] Yield refers to the column-purified product. [c] ee determined by CSP HPLC analysis and values in parenthesis obtained from one quick crystallization of **11aaa** from *i*-PrOH at 25 °C. [d] Reactions were carried out in solvent (0.1 M) with 3 equiv. of **9a** relative to the **7aa** (0.5 mmol) in the presence of 10-mol% of **4u** and 40-mol% of co-catalyst TCA.

L-2-benzhydryl-pyrrolidine **4l**, quinine (Q) **4m**, quinidine (QD) **4n**, cinchonine (C) **4o**, cinchonidine (CD) **4p**, QD-OBn **4q**, OH-QD-OBn **4r**, OH-QD **4s**, CD-NH_2 **4t**, Q-NH_2 **4u** and DHQ-NH_2 **4v** as catalysts and TCA, TFA or 3,5-DNBA as co-catalysts for the cascade asymmetric M-A reaction of **7aa** with **9a** in different solvents as demonstrated in Chart 2 and Table S1–S4 (see ESI†). Among these catalysts **4c–v** tested for cascade asymmetric M-A reaction, 10-mol% of 9-amino-9-deoxyepiquinine (**Q-NH_2**) **4u** with 40-mol% of trichloroacetic acid (TCA) showed better results compared to other catalysts as shown in Table S1–S4 and Table 2, entry 3.[6] Cascade M-A reaction of **7aa** and **9a** in THF under **Q-NH_2**/TCA **4u**-catalysis furnished the Michael product (–)-**10aaa** in 60% yield with only 8% ee and cascade M-A product (+)-**11aaa** in 40% yield with 55% ee, which is enriched to 92% ee with 60–70% yield after one quick crystallization from isopropanol at 25 °C (Table 2, entry 3). We envisioned the optimized condition to be 25 °C in DMSO under 30-mol% L-proline **4a**-catalysis or at 25 °C in THF under 10-mol% **Q-NH_2**/TCA **4u**-catalysis to furnish both enantiomers of highly substituted M-A product (–)-**11aaa** and (+)-**11aaa** in 70/40% yield with 86–92% ee respectively (Table 2). The absolute configuration of products (–)-/(+)-**11aaa** prepared under L-/D-proline-catalysis was established by comparison with the proline-catalyzed Hajos-Parrish-Eder-Sauer-Wiechert reaction.[4,7]

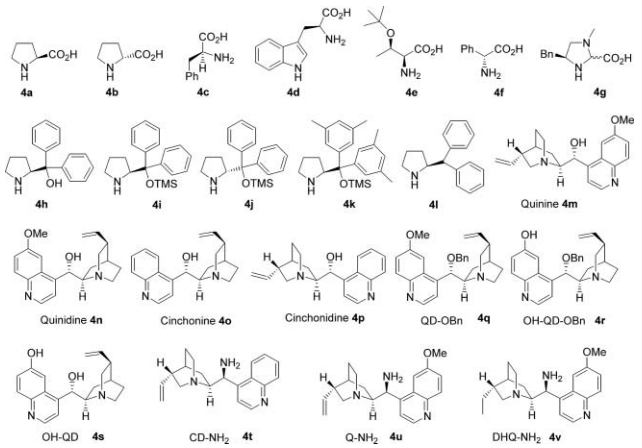
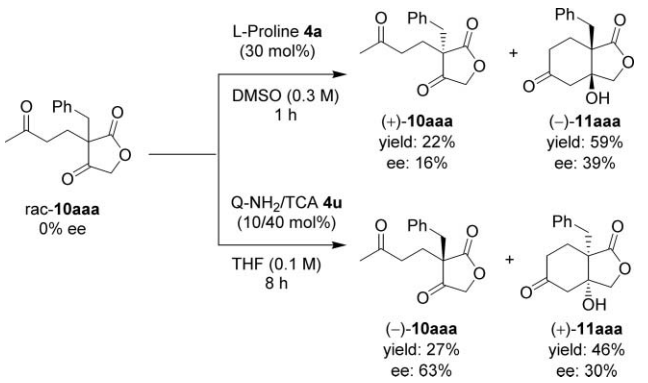


Chart 2 Library of catalysts screened for the cascade asymmetric M-A reaction.

Observation of kinetic resolution in the asymmetric cascade Michael-aldol reactions

Next, we investigated the possibility of kinetic resolution in the amino acid **4a–b** or amine/acid **4u** catalyzed cascade asymmetric M-A reaction of **7aa** and **9a** at the optimized conditions, because ee of Michael adduct is not similar as compared to aldol product from cascade M-A reactions. Treatment of racemic (±)-**10aaa** with 30 mol% of (*S*)-**4a** in DMSO at 25 °C for 1 h furnished (–)-**11aaa** in 59% yield with 39% ee. This product was accompanied by recovered (+)-**10aaa** in 22% yield with 16% ee (see Scheme 2). In a similar manner, treatment of racemic (±)-**10aaa** with 10/40 mol% of **Q-NH_2**/TCA **4u** in THF at 25 °C for 8 h resulted in the formation of (+)-**11aaa** in 46% yield with 30% ee and also recovered (–)-**10aaa** in 27% yield with 63% ee (see Scheme 2). Overall notable kinetic resolution was achieved by means of an amino acid **4a** or amine/acid **4u**-catalysis in cascade



Scheme 2 Observation of kinetic resolution in the cascade M-A reaction

M-A reactions at the ambient conditions. The pronounced kinetic resolution observed in the aldol reaction inspired us to study the enantioselective cascade Michael-aldol annulation reaction with variety of 3-alkyl-tetronic acids.

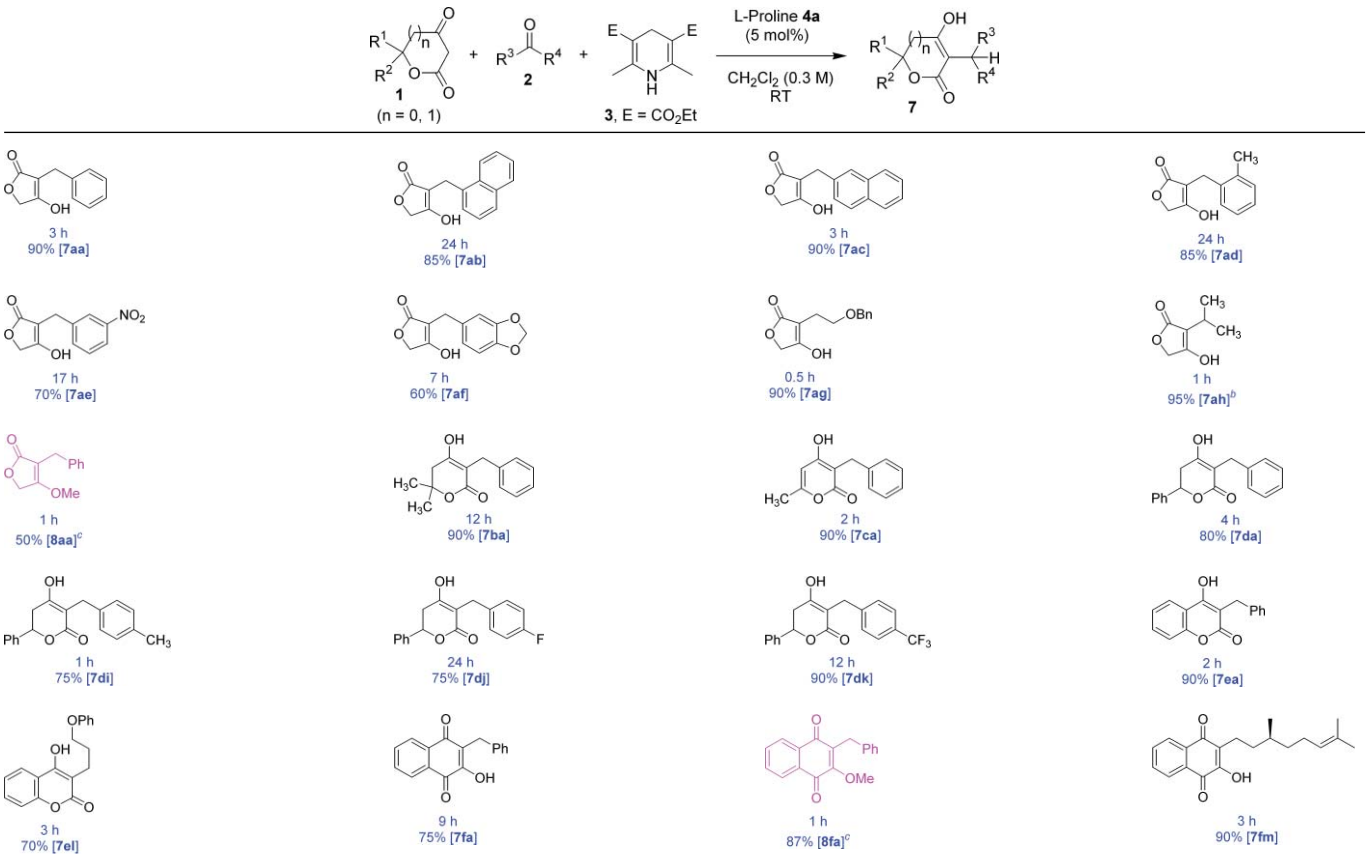
Diversity-oriented high-yielding synthesis of TCRA products 7aa–7fm

With the optimized reaction conditions in hand, the scope of the amino acid- and amine/acid-catalyzed cascade TCRA and asymmetric M-A reactions was investigated. A series of functionalized cyclic β-keto-lactones **1a–f** were reacted with 3 equiv. of aldehydes/ketones **2a–m** and 1 equiv. of organic hydride **3** catalyzed by 5-mol% of L-proline **4a** at 25 °C in CH_2Cl_2 (Table 3). TCRA reaction of tetronic acid **1a** and **3** with neutral, electron-withdrawing and electron-donating substituted benzaldehydes **2a–f** were generated expected products **7aa**–**af** with excellent yields (Table 3). Interestingly, TCRA reaction of benzyloxyacetaldehyde **2g** with **1a** and **3** under **4a**-catalysis furnished the **7ag** as major product with 90% yield (Table 3). Fascinatingly, reaction of tetronic acid **1a** with acetone **2h** under **4a**-catalysis furnished the **7ah** as major single product (Table 3). Interestingly, TCRA reaction of substituted 4-hydroxy-pyran-2-ones **1b–e** with **2a–l** and **3** under **4a**-catalysis furnished the expected 3-alkyl-4-hydroxy-pyran-2-ones **7** with very good yields (Table 3). In continuation, we also tested 2-hydroxy-[1,4]naphthoquinone **1f** as CH-acid source in TCRA reactions. Reaction of **1f** with **2a**/**2m** and **3** under **4a**-catalysis furnished the expected 3-alkyl-2-hydroxy-[1,4]naphthoquinones **7** with good yields as shown in Table 3. To test the reactivity of enolic OH in cascade TCRA products, we treated TCRA product **7aa** with 15 equiv. of ethereal diazomethane at 25 °C for 0.5–1.0 h to furnish the *O*-methylated product **8aa** in good yields through self-catalysis as shown in Table 3. Generality of the self-catalyzed chemoselective *O*-methylation was further confirmed by one more example using **7fa** to furnish the expected **8af** in 87% yield.

The results in Table 3 demonstrate the broad scope of this cascade TCRA methodology covering a structurally diverse group of cyclic β-keto-lactones **1a–f**, aldehydes **2a–m** and ketone **2h** with many of the yields obtained being very good, or indeed better, than previously published two-step alkylation reactions.[2]

TCRA product **7aa** and analogues **7ab**–**ah** are important compounds for the treating HIV and other retroviruses (**D**),[1g] and also for the synthesis of caspase inhibitor (**E**)[1h] and TCRA

Table 3 High-yielding synthesis of cascade TCRA products **7**[a]



[a] Reactions were carried out in CH_2Cl_2 (0.3 M) with 3 equiv. of **2** relative to the **1** and **3** (0.5 mmol) in the presence of 5-mol% of catalyst **4a**. Yield refers to the column-purified product. [b] Acetone **2h** used as solvent and reagent. [c] TCRA compound **7** were reacted with 15 equiv. of ethereal diazomethane and stirred at 25 °C for 0.5–1 h.

products **7ba**–**dk** are directly useful compounds as HIV-1 and HIV-2 protease inhibitors, antiviral/antibacterial agents (**F**),[1i–1j] and hepatitis C virus polymerase inhibitor (**G**).[1k] TCRA products **7ea**/**el** and analogues are useful as inhibitors of vitamin K epoxide reductase (**H**),[1l] reducing the prothrombin content of the blood (**I**)[1m] and HIV-1 protease inhibitor (**J**).[1n] Products **7fa**, **7fm** and **8fa** are useful compounds as treating Huntington's disease (**M**),[1q] *anti*-bacterial, antiviral, and pesticidal compounds (**N**)[1r] emphasizing the value of this novel TCRA approach to the pharmaceuticals and agrochemicals.

Applications of TCRA products

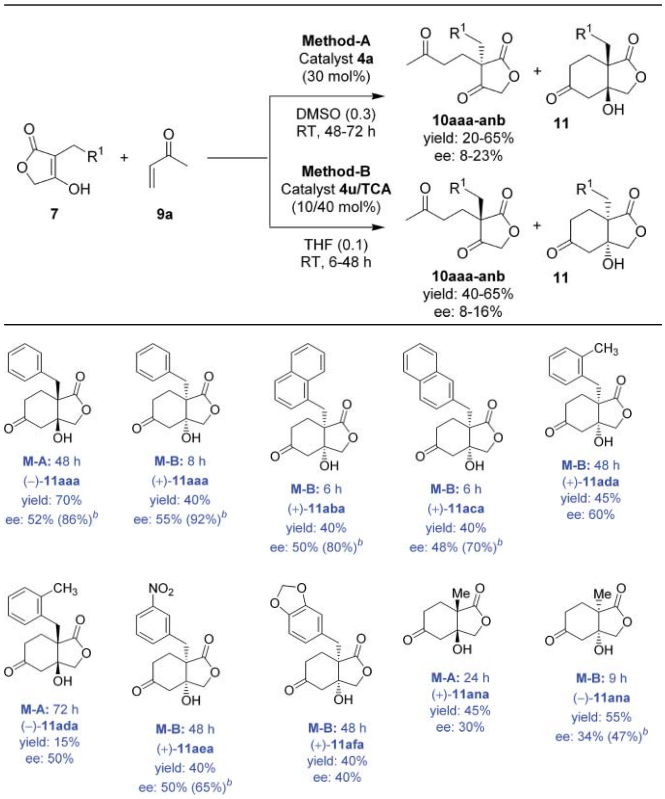
Diversity-oriented asymmetric synthesis of cascade M-A products 11aaa–11ana

With natural products synthesis and pharmaceutical applications in mind, we further extended the utilization of TCRA products in the asymmetric synthesis of functionalized tetrahydro-isobenzofuran-1,5-diones **11**/**12** *via* cascade M-A reactions of **7aa**–**an** and **9a–b** under **4a**- or **4u**-catalysis in one-pot as shown in Table 4.[8] All expected chiral tetrahydro-isobenzofuran-1,5-diones **11**/**12** were furnished in good yields with good to moderate ee's from the reaction of **7** with **9** under **4a** or **4u**-catalysis (see Table 4). Interestingly, **Q-NH$_2$**/TCA **4u**-catalyzed M-A reaction of 4-hydroxy-3-naphthalen-1-ylmethyl-5*H*-furan-2-one **7ab** with 3 equiv. of freshly distilled methyl vinyl ketone **9a** in THF furnished the expected Michael-alcohol product (+)-**11aba** in 40% yield with 80% ee and which is accompanying with Michael adduct **10aba** in 60% yield with 13% ee at 25 °C for 6 h (Table 4, entry 3). A series of 4-hydroxy-3-alkyl-5*H*-furan-2-one **7ac**–**an** were reacted with 3.0 equiv. of methyl vinyl ketone **9a** catalyzed by 30 mol% of L-proline **4a** at 25 °C in DMSO for 24–72 h or 10 mol% of **Q-NH$_2$**/TCA **4u** at 25 °C in THF for 6–48 h (Table 4). All expected bicyclic-alcohols of M-A products **11aca**–**11ana** were obtained in good yields and ee's as shown in Table 4. Hydrolysis of bicyclic-alcohol (+)-**11aaa** obtained from **4u** catalysis with *p*-TSA in C_6H_6 at 80 °C for 1–2 h furnished the expected bicyclic-ketone (–)-**12aaa** in 70% yield with 92% ee as shown in Table 5, entry 1. In a similar manner, we have prepared two more bicyclic-ketones (–)-**12ana**/(+)-**12ana** in 92% yield with 30–47% ee as shown in Table 5, entries 2–3.

Asymmetric synthesis of the key White intermediate for the synthesis of trisporic acids A–B

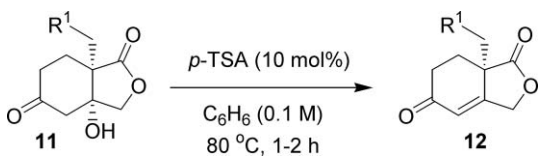
Interestingly, L-proline **4a**-catalyzed cascade M-A reaction of 4-hydroxy-3-benzyl-5*H*-furan-2-one **7aa** with 3 equiv. of freshly

Table 4 Synthesis of chiral cascade M-A products **11**[a]



[a] Yield refers to the column-purified product. [b] ee determined by CSP HPLC analysis and values in paranthesis are obtained from one quick crystallization of **11** from *i*-PrOH at 25 °C.

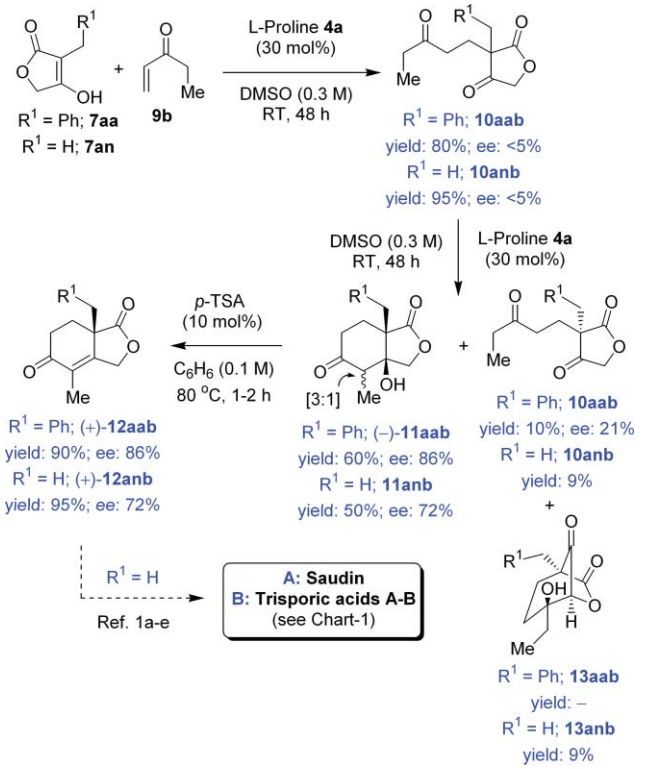
Table 5 Synthesis of chiral bicyclic-ketones **12**[a]



Entry	R^1	Products	Yield (%)[b]	ee (%)[c]
1	Ph	(–)-**12aaa**	70	92
2	H	(–)-**12ana**	92	47
3	H	(+)-**12ana**	92	30

[a] Reactions were carried out in benzene (0.1 M) with 10 mol% of *p*-TSA as catalyst. [b] Yield refers to the column purified product. [c] Ee determined by CSP HPLC analysis.

distilled ethyl vinyl ketone **9b** in DMSO at 25 °C for 48 h furnished the only Michael adduct **10aab** in 80% yield with <5% ee, which on further treatment with 30 mol% of L-proline **4a** in DMSO at 25 °C for 48 h furnished the expected cascade M-A product (–)-**11aab** in 60% yield with 86% ee through kinetic resolution and which is accompanying with unreacted Michael adduct **10aab** in 10% yield with 21% ee (see Scheme 3). In a similar manner, L-proline **4a**-catalyzed cascade M-A reaction of 4-hydroxy-3-methyl-5*H*-furan-2-one **7an** with 3 equiv. of freshly distilled ethyl vinyl ketone **9b** in DMSO at 25 °C for 48 h furnished the Michael adduct

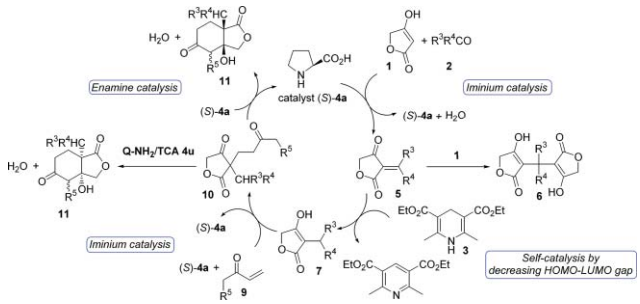


Scheme 3 Asymmetric synthesis of the key White intermediate and analogues for the chiral synthesis of trisporic acids **A–B**.

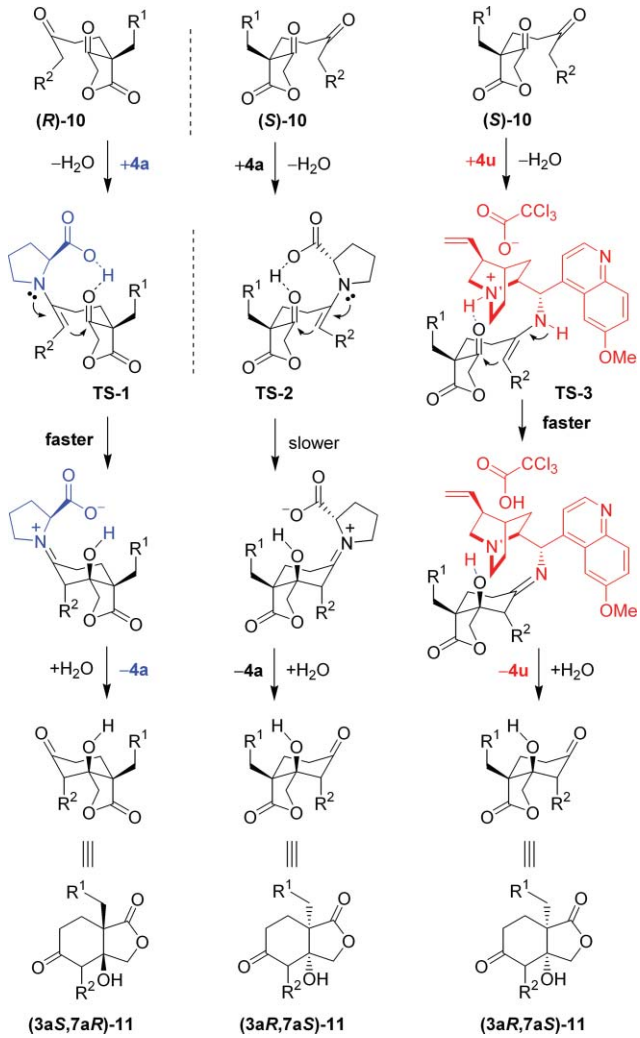
10anb in 95% yield with <5% ee, which on further treatment with 30 mol% of L-proline **4a** in DMSO at 25 °C for 48 h furnished the cascade M-A product **11anb** in 50% yield with 72% ee through kinetic resolution and which is accompanying with 1 : 1 mixture of unreacted Michael adduct **10anb** and new product **13anb** in 18% yield (see Scheme 3). Unfortunately, we are not able to separate these two compounds through column chromatography or chiral HPLC. Hydrolysis of chiral bicyclic-alcohols **11aab**/**11anb** under *p*-TSA-catalysis in C_6H_6 at 80 °C for 1–2 h furnished the expected bicyclic-ketones (+)-**12aab**/(+)-**12anb** in 90/95% yield with 86/72% ee, respectively as shown in Scheme 3.[9] The absolute configuration of products (+)-**12aab**/(+)-**12anb** were established by comparison with the Edmundo A. Rúveda's chiral resolution of the key White intermediate for the synthesis of trisporic acids **B**.[9b] Chiral bicyclic-ketone (+)-**12anb** and their analogues would be suitable intermediates for the asymmetric total synthesis of natural products saudin **A**, trisporic acids **B**, anti-ulcerogenic compound (+)-cassiol and fraxinellonone and its related analogues as shown in Scheme 3.[1a–1e,9]

Mechanistic insights

The possible mechanism for L-proline- or **Q-NH$_2$**/TCA-catalyzed enantioselective synthesis of cascade products **7**, **10** and **11** through the reaction of tetronic acid **1a**, aldehydes/ketones **2**, Hantzsch ester **3** and alkyl vinyl ketone **9** is illustrated in Schemes 4 and 5. In the first step of cascade TCRA reaction, the catalyst (*S*)-**4a** activates component **2** by most likely iminium ion formation, which then selectively adds to the tetronic acid **1a** *via* a Mannich and retro-Mannich type reaction to generate active olefin **5**.[5] The following second step is hydrogenation of active olefin **5** by



Scheme 4 Proposed catalytic cycle for the double cascade reactions.



Scheme 5 Proposed transition states for the asymmetric reactions.

Hantzsch ester **3** to produce **7** through self-catalysis by decreasing HOMO–LUMO energy gap between **3** and **5** respectively.[5] In the subsequent third step or first step of cascade M-A reaction, Michael addition of **7** to alkyl vinyl ketone **9** *via* most likely iminium ion activation leads to the formation of Michael adduct **10** with less enantioselective fashion (≤5% ee). In the fourth step, (*S*)-**4a** or **Q-NH$_2$**/TCA **4u** catalyzed the asymmetric intramolecular aldol condensation of **10** *via* enamine catalysis and ee's of the desired bicyclic-alcohols **11** were obtained through kinetic resolution.

The observed high enantioselectivity in cascade **11** products through kinetic resolution can be explained as illustrated in Scheme 5. L-Proline **4a**-catalyzed Michael addition of **7** to alkyl vinyl ketone **9** furnished the Michael adducts (*R*)-**10** and (*S*)-**10** with <5% ee, which on further reaction of amino acid (*S*)-**4a** with both ketones (*R*)-**10** and (*S*)-**10** generates the enamines with almost similar rates as shown in Scheme 5. Intramolecular aldol condensation of enamine generated from (*R*)-**10** will be a faster reaction compared to enamine generated from (*S*)-**10** as shown in **TS-1** and **TS-2** based on the strong/weak hydrogen bonding interactions, respectively (see Scheme 5). *In situ* hydrolysis of imines generated from **TS-1** and **TS-2** with H_2O furnished the bicyclic-alcohols (3a*S*,7a*R*)-**11** and (3a*R*,7a*S*)-**11** respectively and observed high ee of (3a*S*,7a*R*)-**11** is directly due to the faster reaction rate in **TS-1**. In a similar manner, intramolecular aldol condensation of enamine generated from (*S*)-**10** with **Q-NH$_2$**/TCA **4u** will be a faster reaction compared to enamine generated from (*R*)-**10** as shown in **TS-3** based on the hydrogen bonding interactions and steric hindrance, respectively (see Scheme 5). *In situ* hydrolysis of imine generated from **TS-3** with H_2O furnished the bicyclic-alcohol (3a*R*,7a*S*)-**11** and observed high ee of (3a*R*,7a*S*)-**11** is directly due to the faster reaction rate in **TS-3**. Stereoselective hydrogen bonding interactions are main controlling factor than steric strain control in biomimetic cascade asymmetric M-A reactions, because ee of M-A product **11** is controlled by co-catalyst in **4u**-catalysis. Presently observed high enantioselectivity in cascade M-A reactions through kinetic resolution can be easily understood by rate differences in **TS-1** to **TS-3**, which may needs to get support from the high level DFT calculations.

Conclusions

In summary, this is the first time we have developed the L-proline **4a**- or **Q-NH$_2$**/TCA **4u**-catalyzed asymmetric cascade M-A reaction of 4-hydroxy-3-alkyl-5*H*-furan-2-ones with alkyl vinyl ketone at the ambient conditions. The asymmetric M-A reaction proceeds in good yields with high selectivity using L-proline or **Q-NH$_2$**/TCA as the catalyst through kinetic resolution. Furthermore, we have demonstrated the application of TCRA and M-A reactions in the synthesis of pharmaceutically useful molecules and natural products. Presently developed combination of cascade TCRA and M-A reactions will be suitable to synthesize library of **12anb** for the total synthesis of biologically important natural products and their analogues. Further work is in progress to utilize chiral bicyclic-alcohols as intermediates for the asymmetric synthesis of bio-active molecules.

Experimental

General methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. *In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses.* The coupling constants *J* are given in Hz. Column chromatography was performed using Acme's silica gel

(particle size 0.063–0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. LCMS mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010A mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

Materials

All solvents and commercially available chemicals were used as received.

General experimental procedures for the cascade TCRA and M-A reactions

Amino acid-catalyzed cascade three-component reductive alkylation (TCRA) reactions with cyclic β-keto-lactones

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the aldehyde **2**, 0.3 mmol of CH acid **1**, and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of solvent, and then the catalyst amino acid **4a** (0.015 mmol) was added, and the reaction mixture was stirred at 25 °C for the time indicated in Table 3. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade products **7aa**–**7fm** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

General procedure for the synthesis of 3-benzyl-4-methoxy-5*H*-furan-2-one 8aa

In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of 4-hydroxy-3-benzyl-5*H*-furan-2-one **7aa** in 1.0 mL of ether at 0 °C added an excess ethereal solution of diazomethane and the reaction mixture was stirred at room temperature for the 0.5 h. After evaporation of the solvent and excess diazomethane completely in a fume hood, the crude reaction mixture was directly loaded on silica gel column without aqueous work-up and pure products **8aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Preparation for racemic Michael products 10 with triethylamine-catalysis

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 4-hydroxy-3-alkyl-5*H*-furan-2-one **7** and 0.9 mmol of methyl vinyl ketone **9a** with a catalytic amount of triethylamine in 1.0 mL of THF solvent and the reaction mixture was stirred at 25 °C for 6–48 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **10** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Preparation of racemic cascade Michael-aldol products 11 with DL-β-phenylalanine-catalysis

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 4-hydroxy-3-alkyl-5*H*-furan-2-one **7** and 0.9 mmol of methyl vinyl ketone **9a** with a catalytic amount of DL-β-phenylalanine in 1.0 mL of THF solvent and the reaction mixture was stirred at 25 °C for 6–48 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **11** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Amino acid-catalyzed asymmetric cascade Michael-aldol reactions

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 4-hydroxy-3-alkyl-5*H*-furan-2-one **7** and 0.9 mmol of methyl vinyl ketone **9a** was added 1.0 mL of DMSO solvent, and then the catalyst L-proline **4a** (0.09 mmol) was added, 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 ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure cascade M-A products **11** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Q-NH_2/TCA-catalyzed asymmetric cascade Michael-aldol reactions

In an ordinary glass vial equipped with a magnetic stirring bar, to **Q-NH_2 4u** (0.05 mmol) and TCA (32 mg, 0.2 mmol) in THF (5.0 mL) were added and stirred at 25 °C for 10 min then 0.5 mmol of 4-hydroxy-3-alkyl-5*H*-furan-2-one **7** and 1.5 mmol of methyl vinyl ketone **9a** was added, and the reaction mixture was stirred at 25 °C for 6–48 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure cascade M-A products **11** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

General procedure for the hydrolysis of cascade Michael-aldol products

A solution of bicyclic alcohol compound **11** (0.5 mmol) and *p*-TSA (0.05 mmol) in dry benzene (3.0 mL) was stirred at 80 °C for 1 h. After cooling, the reaction mixture washed with aqueous sodium bicarbonate solution and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **12** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Many of the cascade products **7**, **8**, **10** and **11** are commercially available, or have been described previously, and their analytical data match literature values. New compounds were characterized

on the basis of IR, ^{1}H and ^{13}C NMR and analytical data (see ESI†).

Acknowledgements

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]. MK thanks Council of Scientific and Industrial Research (CSIR), New Delhi for his SRF fellowship.

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