Direct amino acid-catalyzed cascade biomimetic reductive alkylations: application to the asymmetric synthesis of Hajos–Parrish ketone analogues†

Dhevalapally B. Ramachary* and Mamillapalli Kishor

Received 12th May 2008, Accepted 11th July 2008
First published as an Advance Article on the web 12th August 2008
DOI: 10.1039/b807999d

A direct amino acid-catalyzed chemo- and enantioselective process for the double cascade synthesis of highly substituted 2-alkyl-cyclopentane-1,3-diones, 2-alkyl-3-methoxy-cyclopent-2-enones and Hajos–Parrish (H–P) ketone analogs is presented *via* reductive alkylation chemistry. For the first time, we have developed a single-step alkylation of cyclopentane-1,3-dione with aldehydes/ketones and a Hantzsch ester through an organocatalytic reductive alkylation strategy. A direct combination of amino acid-catalyzed cascade olefination–hydrogenation and cascade Robinson annulations of cyclopentane-1,3-dione, aldehydes/ketones, a Hantzsch ester and methyl vinyl ketone furnished the highly functionalized H–P ketone analogues in good to high yields and with excellent enantioselectivities. Many of the reductive alkylation products have shown direct applications in pharmaceutical chemistry.

Introduction

Cascade and multi-component reactions are processes in which three or more easily accessible components are combined together in a single reaction vessel to produce a functionalized product displaying features of all inputs; thus, the processes offer greater possibilities for molecular diversity per step with a minimum of synthesis time, solvents and effort.[1] As cascade reactions are one-pot reactions, they are easier to carry out than classical multi-step syntheses. Combined with high-throughput library screening, this cascade strategy was an important development for drug discovery in the context of rapid identification and optimization of biologically active lead compounds. Libraries of small-molecule organic compounds are perhaps the most desired class of potential drug candidates. With a small set of starting materials, very large libraries can be built up within a short time, which can then be used for research on medicinal substances. In spite of the significant useful attributes of cascade and multi-component reactions for modern organic chemistry and their suitability for building up large compound libraries, these reactions have received limited interest over the past fifty years. However, in the last decade, with the introduction of high-throughput biological screening, the importance of cascade and multi-component reactions for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focused especially on the design and development of multi-component procedures for the generation of libraries of highly functionalized compounds.[1]

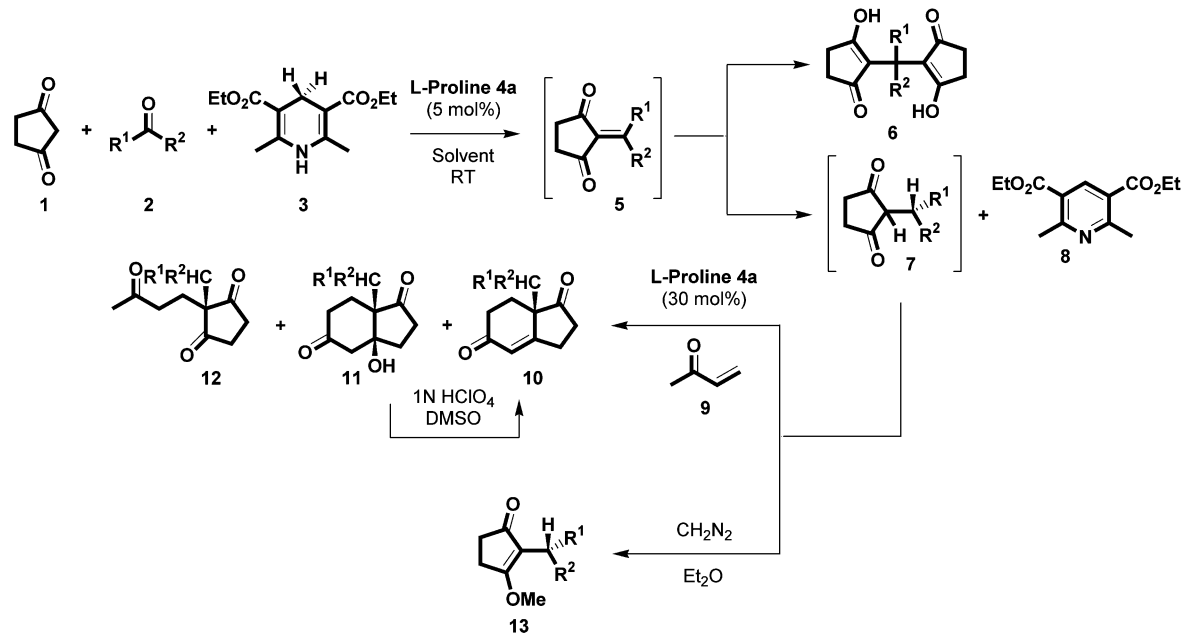
In continuation of the development of novel biomimetic cascade reactions, recently, amino acid- or amine-catalyzed cascade and multi-component reactions have attracted a considerable amount of attention from chemists and biologists. Amino acid- or amine-catalyzed cascade and multi-component reactions involve two or more bond-forming transformations that take place under the same reaction conditions from simple starting materials catalyzed by small molecular units of metal-free proteins.[2] Amino acid/amine-catalyzed reactions have in the past few years emerged as a powerful synthetic tool for the construction of highly functionalized, complex and optically active compounds,[3] in particular, amino acid-catalyzed cascade and multi-component reactions emerging as ideal synthetic strategies for the synthesis of highly functionalized compounds and drug like small molecules in one pot, mimicking biological reactions.[4]

As part of our research program to engineer direct amino acid/amine-catalyzed cascade, multi-component or organo-click reactions,[4a–i] herein we report the first organocatalytic asymmetric chemo-selective direct cascade olefination–hydrogenation (O–H), olefination–hydrogenation–Robinson annulation (O–H–RA) and olefination–hydrogenation–etherfication (O–H–E) reactions that produce very useful drug synthons, 2-alkyl-cyclopentane-1,3-diones **7**, Hajos–Parrish (H–P) ketone analogs **10** and 2-alkyl-3-methoxy-cyclopent-2-enones **13** from commercially available cyclopentane-1,3-dione **1**, aldehydes or ketones **2**, Hantzsch ester **3**, methyl vinyl ketone **9** and amino acid **4** as shown in Scheme 1. 2-Alkyl-cyclopentane-1,3-diones **7**, H–P ketone analogues **10** and 2-alkyl-3-methoxy-cyclopent-2-enones **13** are attractive intermediates in the synthesis of natural products and in medicinal chemistry,[5] whilst 2-alkyl-cyclopentane-1,3-diones **7** and 2-alkyl-3-methoxy-cyclopent-2-enones **13** have broad utility in pharmaceutical chemistry[6] and are excellent starting materials in natural product synthesis as shown in Chart 1. Hence, their preparation has continued to attract considerable synthetic interest in developing new methods for their syntheses.[7]

Interestingly, there is no direct methodology for the synthesis of useful 2-alkyl-cyclopentane-1,3-diones **7** and only two-step methods are known to prepare them.[7] Recently, Paquette *et al.* developed the two-step synthesis of 2-alkyl-cyclopentane-1,3-diones **7** in moderate to good yields *via* an *in situ* protection and

School of Chemistry, University of Hyderabad, Hyderabad-500 046, India. E-mail: ramsc@uohyd.ernet.in; Fax: +91-40-23012460

† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. CCDC reference number 674004. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b807999d



Substrates and Catalysts Screened:

2a: R^1 = H, R^2 = C_6H_5
2b: R^1 = H, R^2 = 1-Naphthalenyl
2c: R^1 = H, R^2 = 2-Naphthalenyl
2d: R^1 = H, R^2 = 4-OHC_6H_4
2e: R^1 = H, R^2 = 3-OHC_6H_4
2f: R^1 = H, R^2 = 2-OHC_6H_4
2g: R^1 = H, R^2 = 2-$(OCH_2CH{=}CMe_2)C_6H_4$
2h: R^1 = H, R^2 = 3-$NO_2C_6H_4$
2i: R^1 = H, R^2 = 2-$NO_2C_6H_4$
2j: R^1 = H, R^2 = *trans*-$C_6H_5CH{=}CH$
2k: R^1 = H, R^2 = *trans*-2-$NO_2C_6H_4CH{=}CH$
2l: R^1 = H, R^2 = CH_3
2m: R^1 = H, R^2 = CH_3CH_2
2n: R^1 = H, R^2 = $CH_3CH_2CH_2$
2o: R^1 = H, R^2 = $CH_3CH_2CH_2CH_2$
2p: R^1 = H, R^2 = $CH_3CH_2CH_2CH_2CH_2$
2q: R^1 = H, R^2 = $CH_3CH_2CH_2CH_2CH_2CH_2$
2r: R^1 = H, R^2 = $CH_3CH_2CH_2CH_2CH_2CH_2CH_2$
2s: R^1 = H, R^2 = Me_2CH
2t: R^1 = H, R^2 = Me_2CHCH_2
2u: (*R*)-(+)-Citronellal
2v: (*S*)-(-)-Citronellal
2w: R^1 = R^2 = CH_3
2x: R^1 = R^2 = $-CH_2(CH_2)_3CH_2-$
4a: L-Proline
4b: D-Proline
4c: Benzylamine
4d: Pyrrolidine
4e: Piperidine
4f: Morpholine

Scheme 1 Direct organocatalytic asymmetric cascade O–H, O–H–RA and O–H–E reactions.

deprotection sequence on 2-alkylidene-1,3-diones **5** with thiophenol and Raney nickel, respectively.[7m] As shown in Scheme 1, the well-recognized fact is the inability to arrest olefination reactions involving cyclopentane-1,3-dione **1** and aliphatic or aromatic aldehydes **2** at the mono-addition stage.[8] Very few adducts such as **5** have been isolated.[9] This is because these olefination products **5** are highly reactive Michael acceptors capable of engaging the unreacted cyclopentane-1,3-dione **1** reagent in kinetically rapid l,4-addition to give bis-adducts such as **6**. Also, there is no report on the asymmetric synthesis of higher alkyl substituted H–P ketone analogues **10**. This has prompted us to investigate the cascade synthesis of very useful 2-alkyl-cyclopentane-1,3-diones **7**, H–P ketone analogues **10** and 2-alkyl-3-methoxy-cyclopent-2-enones **13** in a single step through mild amino acid-catalysis.

We consequently set out to develop an amino acid-catalyzed asymmetric cascade synthesis of higher alkyl analogues of H–P ketones **10** from simple starting materials, which have not been prepared in the past. In this article, we present the development and application of the amino acid-catalyzed reductive alkylation of cyclopentane-1,3-dione **1** through cascade O–H reaction of reactive 1,3-dione **1**, aldehydes or ketones **2** and Hantzsch ester **3**. Furthermore, we will present mechanistic insight into the reaction course, applying a new concept of self-catalysis leading to an understanding of the cascade O–H reaction with utilization of calculations.

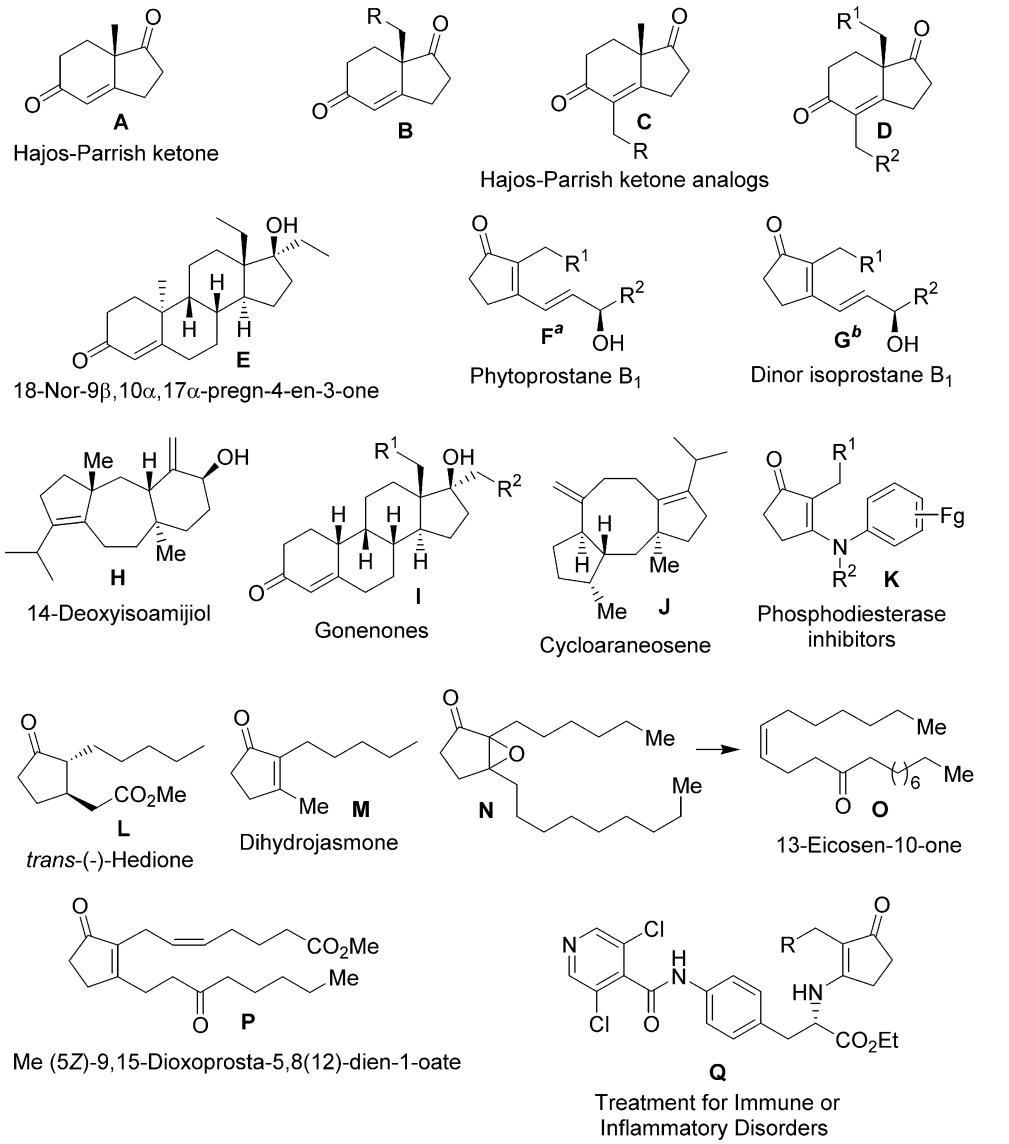
We imagine that an amino acid or amine would catalyze the cascade olefination reaction of 1,3-dione **1** with an aldehyde or ketone **2** to form substituted 2-alkylidene-cyclopentane-1,3-diones **5**, which are very reactive intermediates and further undergo chemoselective reactions with both 1,3-dione **1** and Hantzsch ester **3** to produce bis-adducts **6** and hydrogenated 2-alkyl-cyclopentane-1,3-diones **7**, respectively, based on reaction conditions. Amino acid-catalyzed Robinson annulation of products **7** with methyl vinyl ketone **9** furnishes the H–P ketones **10** and alcohols **11** in good yield with very good enantioselectivity, and alcohol **11** would be converted into ketone **10** without losing enantioselectivity as shown Scheme 1.

Results and discussion

Direct amino acid-catalyzed cascade reductive alkylation of cyclopentane-1,3-dione: reaction optimization

We initiated our preliminary investigation by the *in situ* reduction of 2-benzylidene-cyclopentane-1,3-dione **5a**‡ with Hantzsch ester **3** as shown in Table 1. The self-catalyzed reaction of cyclopentane-1,3-dione **1** with 3 equiv of benzaldehyde **2a** furnished the

‡ In all compounds denoted **5x**, **6x**, **7x**, **10x**, **11x**, **12x** and **13x**, **x** is incorporated from reactant aldehydes or ketones **2**.



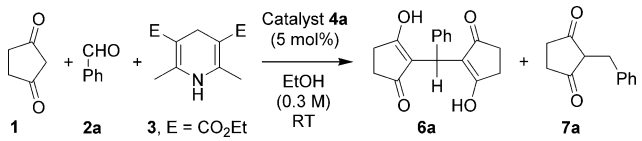
[a] **PPB$_1$ type I:** $R^1 = (CH_2)_6CO_2H$, $R^2 = CH_2CH_3$; **PPB$_1$ type II:** $R^1 = CH_3$, $R^2 = (CH_2)_7CO_2H$
[b] **DIPB$_1$ type III:** $R^1 = (CH_2)_3CO_2H$, $R^2 = (CH_2)_4CH_3$; **DIPB$_1$ type IV:** $R^1 = (CH_2)_3CH_3$, $R^2 = (CH_2)_4CO_2H$

Chart 1 Natural and non-natural products library generated from 2-alkyl-cyclopentane-1,3-diones.

only unexpected bis-adduct **6a** without the expected olefination product **5a** (Table 1, entry 1). The same reaction under proline-catalysis also furnished the only bis-adduct **6a** without product **5a** with reduced reaction time (Table 1, entry 2). Interestingly, self-catalyzed reaction of cyclopentane-1,3-dione **1** and 2 equiv of benzaldehyde **2a** with Hantzsch ester **3** furnished the bis-adduct **6a** and expected reductive alkylation product **7a** with 80% overall yield in 1 : 4.3 ratio respectively after 24 h at 25 °C (Table 1, entry 3). The self-catalyzed reductive alkylation reaction with 3 equiv of benzaldehyde **2a** furnished the product **7a** in 90% yield after 24 h at 25 °C (Table 1, entry 4). Interestingly, the same reaction under proline-catalysis furnished the expected reductive alkylation product **7a** with 90% yield after 12 h at 25 °C in EtOH as shown in Table 1, entry 5. These preliminary results prompted us to investigate the solvent and catalyst effect on *in situ* trapping of olefination product of cyclopentane-1,3-dione **1** with benzaldehyde **2a** through biomimetic hydrogenation as shown in Table 2.

After preliminary demonstration of the amino acid-promoted cascade O–H reactions for the generation of cascade product **7a** from **1**, **2a** and **3**, we decided to investigate the solvent and catalyst effect on cascade O–H reactions. Interestingly, proline-catalyzed cascade O–H reactions of **1**, **2a** and **3** are solvent and catalyst dependent reactions as shown in Table 2. The cascade O–H reaction of **1**, **2a** and **3** catalyzed by simple amines like benzylamine **4c**, pyrrolidine **4d**, piperidine **4e** and morpholine **4f** in ethanol are not superior compared to self- and proline-catalysis as shown in Table 2, entries 1–4. There is a large amount of solvent effect on

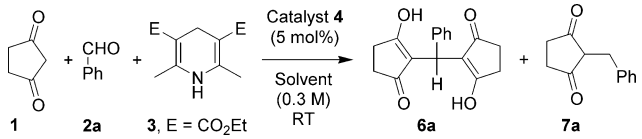
Table 1 Preliminary study for reaction optimization[a]



Entry	Catalyst **4a** (5 mol%)	Aldehyde **2a** (equiv.)	Hantzsch ester **3** (equiv.)	Time/h	Products **6a**	Yield (%)[b] **7a**
1	—	3.0	—	24	75	—
2	Proline	3.0	—	12	75	—
3	—	2.0	1.0	24	15	65
4	—	3.0	1.0	24	10	90
5	**Proline**	**3.0**	**1.0**	**12**	**10**	**90**

[a] Reactions were carried out in ethanol (0.3 M) with 2.0 to 3.0 equiv of **2a** and 1.0 equiv of **3** relative to **1** (0.3 mmol) in the presence of 5 mol% of catalyst **4a**. [b] Yield refers to the column purified product.

Table 2 Reaction optimization[a]



Entry	Solvent (0.3 M)	Catalyst **4** (5 mol%)	Time/h	Products **6a**	Yield (%)[b] **7a**
1	EtOH	Benzylamine **4c**	24	40	60
2	EtOH	Pyrrolidine **4d**	24	50	50
3	EtOH	Piperidine **4e**	24	50	50
4	EtOH	Morpholine **4f**	24	50	50
5	MeOH	Proline **4a**	3	8	88
6	H_2O	Proline **4a**	3	71	26
7	DMSO	Proline **4a**	6	40	60
8	DMF	Proline **4a**	6	40	60
9	CH_3CN	Proline **4a**	6	10	88
10	**CH_2Cl_2**	**Proline 4a**	**2**	**7**	**93**
11[c]	CH_2Cl_2	Proline **4a**	6	20	80
12[d]	CH_2Cl_2	**Proline 4a**	6	40	60

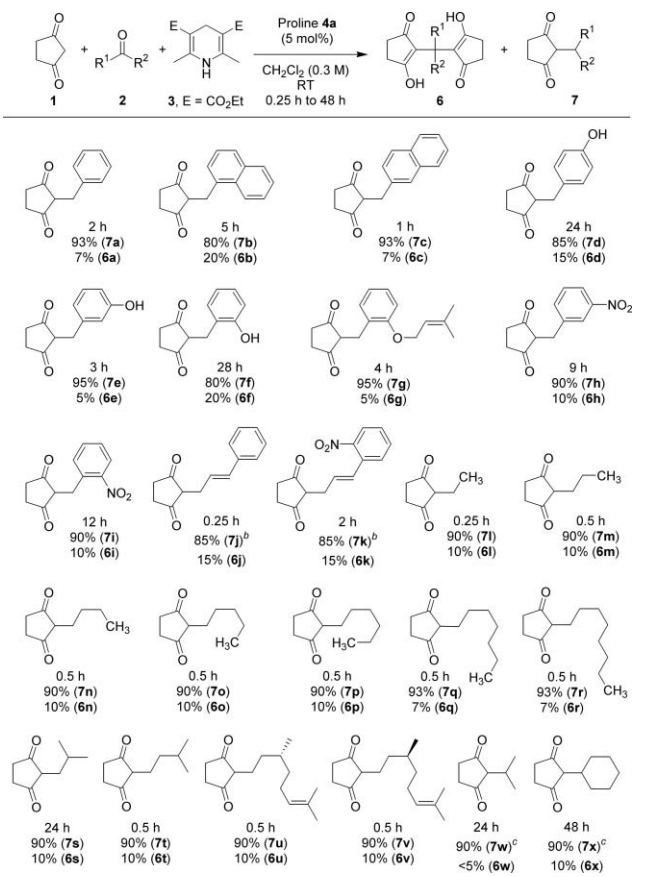
[a] Reactions were carried out in solvent (0.3 M) with 1.0 to 3.0 equiv of **2a** and 1.0 equiv of **3** relative to **1** (0.3 mmol) in the presence of 5 mol% of catalyst **4**. [b] Yield refers to the column purified product. [c] 2.0 Equiv of **2a** was used. [d] 1.0 Equiv of **2a** was used.

the direct proline-catalyzed reductive alkylation or cascade O–H reaction of **1**, **2a** and **3** as shown in Table 2. Proline-catalyzed cascade O–H reactions can be performed in three types of solvents (protic polar, aprotic polar and aprotic non-polar) with moderate to good yields as shown in Table 2. Surprisingly, the cascade O–H reaction of **1**, **2a** and **3** in H_2O furnished the expected hydrogenated product **7a** in 26% yield accompanied by a 71% yield of bis-adduct **6a** after 3 h at 25 °C (Table 2, entry 6). The same cascade reaction under proline-catalysis in CH_2Cl_2 furnished the expected product **7a** in 93% yield after 2 h at 25 °C (Table 2, entry 10). We envisioned the optimized conditions to be mixing the 3 equiv of benzaldehyde **2a** with cyclopentane-1,3-dione **1** and Hantzsch ester **3** at 25 °C in CH_2Cl_2 under 5 mol% of proline-catalysis to furnish the hydrogenated product **7a** in 93% yield (Table 2, entry 10).

Diversity-oriented synthesis of reductive alkylation products 7a–x

With the optimized reaction conditions in hand, the scope of the proline-catalyzed O–H cascade reactions was investigated with cyclopentane-1,3-dione **1**, various aldehydes **2a–v** or ketones **2w–x** and Hantzsch ester **3** as shown in Table 3. A series of aromatic and aliphatic aldehydes **2a–v** (3 equiv) were reacted with cyclopentane-1,3-dione **1** and Hantzsch ester **3** catalyzed by 5 mol% of proline at 25 °C in CH_2Cl_2 (Table 3). The 2-arylmethyl-cyclopentane-1,3-diones **7a–i** and 2-alkyl-cyclopentane-1,3-diones **7j–v** were obtained as single isomers (tautomer) with excellent yields. The cascade reaction of cyclopentane-1,3-dione **1** with naphthalene-1-carbaldehyde **2b** and **3** furnished the reductive alkylation product **7b** as a single tautomer, in 80% yield after 5 h at 25 °C (Table 3). But the same cascade reaction with naphthalene-2-carbaldehyde **2c** and **3** furnished the reductive alkylation product **7c** as a single tautomer, with 93% yield after 1 h at 25 °C (Table 3). Synthesis of 2-arylmethyl-cyclopentane-1,3-diones **7a–i** from **1**, **2a–i** and **3** at 25 °C under proline-catalysis has taken longer reaction times (1–28 h), compared to aliphatic aldehydes **2j–v** as shown in Table 3. Interestingly, proline-catalyzed reductive alkylation reaction of cyclopentane-1,3-dione **1**, α,β-unsaturated aldehydes **2j–k** and Hantzsch ester **3** generated the expected 2-alkyl-cyclopentane-1,3-diones **7j–k** in excellent yields with

Table 3 Chemically diverse libraries of cascade O–H products **7**[a]



[a] Yield refers to the column purified product. [b] A 1 : 2.0 ratio of completely reduced and 1,4-reduction **7j/k** products were formed (see ESI†). [c] Solvent CH_2Cl_2 and ketones **2w/2x** were taken in a 1 : 1 ratio.

moderate chemoselectivity (Table 3). Completely hydrogenated products **7j′/7k′** and 1,4-reduction products **7j/7k** are furnished in a 1 : 2.0 ratio respectively as shown in Table 3. Interestingly, proline-catalyzed cascade reductive alkylation reaction of cyclopentane-1,3-dione **1** with chiral aldehydes **2u–v** and Hantzsch ester **3** furnished the expected single enantiomer of 2-alkyl-cyclopentane-1,3-diones **7u–v** in excellent yields with high stereoselectivity (Table 3). Cascade products (*R*)-(−)-2-(3,7-dimethyl-oct-6-enyl)-cyclopentane-1,3-dione **7u** and (*S*)-(+)-2-(3,7-dimethyl-oct-6-enyl)-cyclopentane-1,3-dione **7v** are generated in 90% yields *via* cascade O–H reaction. Proline-catalyzed cascade reductive alkylation of cyclopentane-1,3-dione **1** was further extended with ketones also as shown in Table 3. Cascade reductive alkylation reaction of cyclopentane-1,3-dione **1** with acetone **2w** or cyclohexanone **2x** and Hantzsch ester **3** under 5 mol% of proline-catalysis furnished the expected single isomers of 2-alkyl-cyclopentane-1,3-diones **7w–x** in excellent yields (Table 3). The results in Table 3 demonstrate the broad scope of this reductive cascade methodology covering a structurally diverse group of aldehydes **2a–v** and ketones **2w–x** with many of the yields obtained being very good, or indeed better, than previously published two-step alkylation reactions.[7] The structure and regiochemistry of 2-alkyl-cyclopentane-1,3-diones **7a–x** were confirmed by X-ray structure analysis on **7i** as shown in Fig. 1.[10]

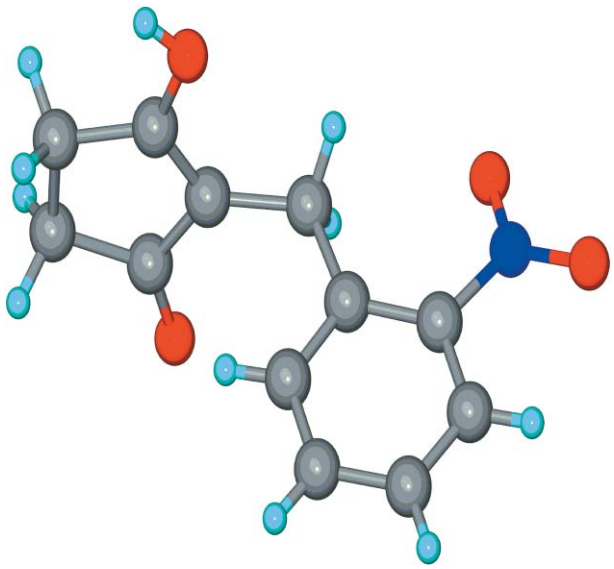


Fig. 1 Crystal structure of 2-(2-nitro-benzyl)-cyclopentane-1,3-dione (**7i**).

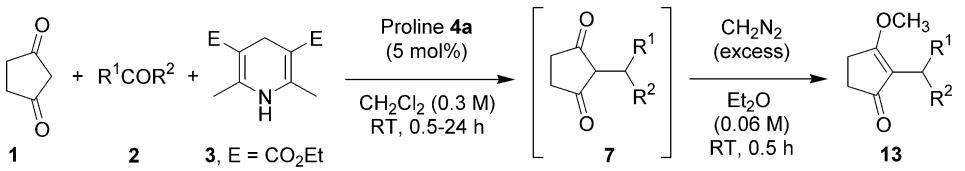
Interestingly, many of the 2-alkyl-cyclopentane-1,3-diones **7a–x** exist in the enol form in both the solid state and solution state, which may be due to the strong intermolecular hydrogen bonding; also, this characteristic is observed in many other 1,3-diketones.[7] The chemical shifts of the C1 and C3 carbon atoms in the isolated, non-hydrogen-bonded enol forms of 2-alkyl-cyclopentane-1,3-diones **7a–x** can hardly be determined in solution, due to the rapid keto–enol and enol–enol tautomerism.[7n] Therefore, in 2-alkyl-cyclopentane-1,3-dione compounds **7a–x**, we observed that ^{13}C NMR shows two of CH_2 carbons α to the carbonyls (*C*=O) including the two carbonyl carbons ($2 \times CH_2$ and $2 \times C$=O) are poor resolution even after 2000 scans on standard sampling. This same kind of ^{13}C NMR pattern was observed for the other 1,3-diketones in the literature due to the rapid keto–enol and enol–enol tautomerism.[7]

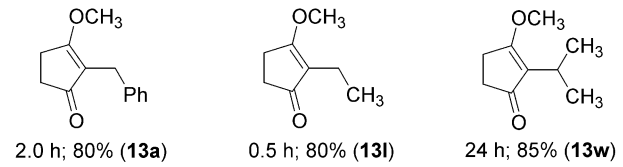
Applications of reductive alkylation products

Chemoselective O-alkylation of 2-alkyl-cyclopentane-1,3-diones

Cascade products 2-alkyl-cyclopentane-1,3-diones **7** are readily transformed into substituted 2-alkyl-3-methoxy-cyclopent-2-enones **13** by treatment with an ethereal solution of diazomethane in one pot as shown in Scheme 2. The highly functionalized 2-alkyl-3-methoxy-cyclopent-2-enone unit is a basic building block for a large number of valuable naturally occurring products.[6l–q] Highly functionalized 2-alkyl-3-methoxy-cyclopent-2-enones **13** have gained importance in recent years as starting materials and intermediates for the synthesis of prostaglandin analogues, which possess a wide range of physiological and pharmacological properties.[6l–q] Long chain 2-alkyl-3-methoxy-cyclopent-2-enones **13** have been successfully utilized as ideal synthons for the synthesis of prostaglandin analogues, which are used for the treatment or prevention of cancer.[6l–q]

Cascade O–H reaction of **1**, **2a** and **3** under 5 mol% of proline-catalysis furnished the substituted 2-benzyl-cyclopentane-1,3-dione **7a** in good yield, which on treatment with ethereal





[a] Yield refers to the column purified product.

Scheme 2 Direct organocatalytic one-pot synthesis of 2-alkyl-3-methoxy-cyclopent-2-enones **13**.[a]

diazomethane at 25 °C for 0.5 h furnished the chemoselectively one-pot O–H–E product 2-benzyl-3-methoxy-cyclopent-2-enone **13a** in 80% yield through self-catalysis as shown in Scheme 2. The acidic or highly enolizable nature of 2-alkyl-cyclopentane-1,3-diones **7** is the main driving force in leading us to observe a highly chemoselective O-alkylation reaction with diazomethane. The generality of the proline/self-catalyzed chemoselective one-pot O–H–E reaction was further confirmed by two more examples using aliphatic acetaldehyde **2l** and acetone **2w** to furnish the expected 2-ethyl-3-methoxy-cyclopent-2-enone **13l** in 80% yield and 2-isopropyl-3-methoxy-cyclopent-2-enone **13w** in 85% yield, respectively as shown in Scheme 2. For pharmaceutical applications, a diversity-oriented library of enones **13** could be generated by using our amino acid/self-catalyzed, chemoselective one-pot O–H–E reaction.

Amino acid-catalyzed asymmetric Robinson annulations

Higher alkyl substituted H–P ketone analogues **10** are very good intermediates for the synthesis of natural products like steroids.[5] Recently, Ali Amjad *et al.* reported in their papers[11] that higher alkyl H–P ketone analogues **10** 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 or conditions (see Chart 2). Interestingly, to the best of our knowledge, there is no report for the asymmetric synthesis of useful higher alkyl substituted H–P ketone analogues **10**. In this paper, we are presenting the asymmetric synthesis of H–P ketone analogs **10** with very good ee and yields *via* amino acid-catalyzed asymmetric RA of 2-alkyl-cyclopentane-1,3-diones **7** with methyl vinyl ketone **9** as shown in Tables 4–5.

Interestingly, L-proline-catalyzed RA reaction of 2-benzyl-cyclopentane-1,3-dione **7a** with 3 equivalents of freshly distilled methyl vinyl ketone **9** in CH_3CN furnished the expected alcohol product **11a** in 60% yield accompanied by Michael adduct **12a** in 26% yield at 25 °C for 6 days (Table 4, entry 1). Hydrolysis of bicyclic-alcohol **11a** obtained from L-proline **4a** catalysis with 1 N $HClO_4$ in DMSO at 90 °C for 1 h furnished the expected bicyclic-ketone (+)-**10a** in 80% yield with 85% ee as shown in Table 4, entry 1. Solvent screening on the direct L-proline-catalyzed RA reaction of **7a** with **9** revealed that DMSO solvent is suitable to achieve high yields and ee's as shown in Table 4. We envisioned the optimized conditions to be mixing the 2-benzyl-cyclopentane-1,3-dione **7a** and 3 equivalents of freshly distilled methyl vinyl ketone **9** at 25 °C in DMSO under 30 mol% of L-proline to furnish the alcohol of H–P ketone analogue **11a** in 67% yield accompanied by Michael adduct **12a** in 33% yield, which on hydrolysis with

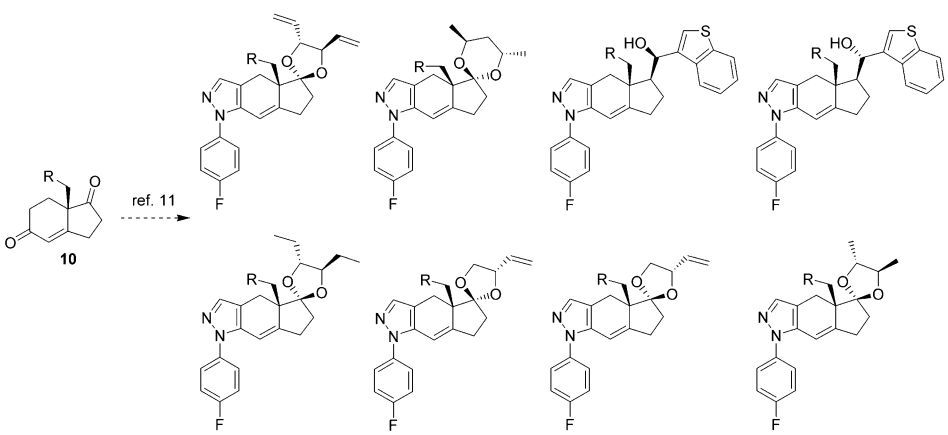
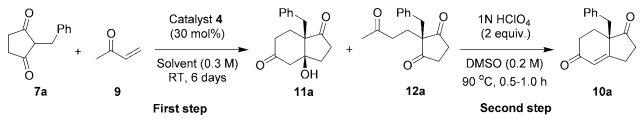


Chart 2 Selective ligand analogues for the human glucocorticoid receptor.

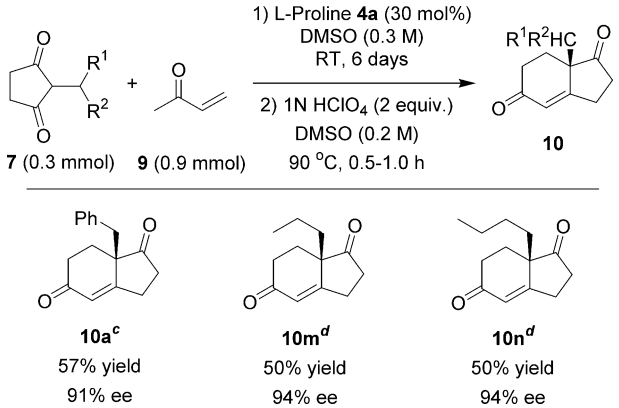
Table 4 Direct amino acid-catalyzed Robinson annulation of **7a** with **9**[a]



Entry	Solvent (0.3 M)	Catalyst **4** (30 mol%)	Yield (%)[b] **11a**	Yield (%)[b] **12a**	Yield (%)[b,c] **10a**	Ee (%)[d] **10a**
1	CH_3CN	**4a**	60	26	80	85
2	DMSO	**4a**	67	33	85	91
3	DMF	**4a**	58	22	80	91
4	DMSO	**4b**	66	34	96	–90

[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv of freshly distilled methyl vinyl ketone **9** in the presence of 30 mol% of proline **4**. [b] Yield refers to the column purified product. [c] Yield of **10a** is based on **11a**. [d] Ee determined by HPLC analysis.

Table 5 Organocatalytic asymmetric synthesis of H–P ketone analogues **10**[a,b]



[a] See Experimental Section. [b] Yield refers to the column purified product and ee determined by HPLC analysis. [c] Michael adduct **12a** were isolated in 33% yield. [d] Michael adducts **12m** and **12n** were isolated in 40–50% yields respectively.

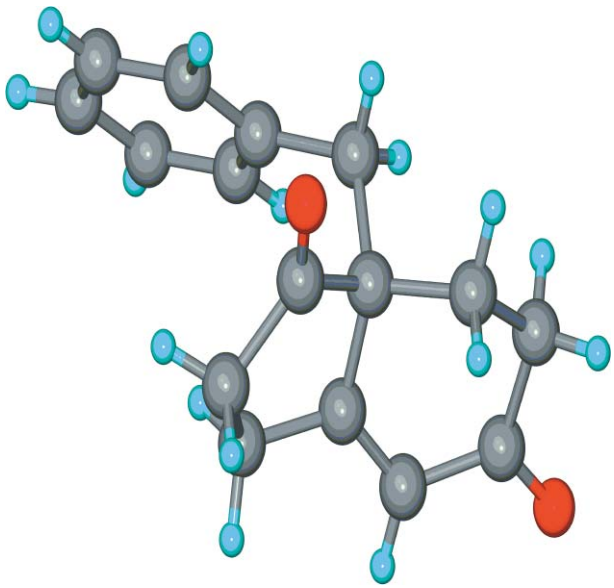


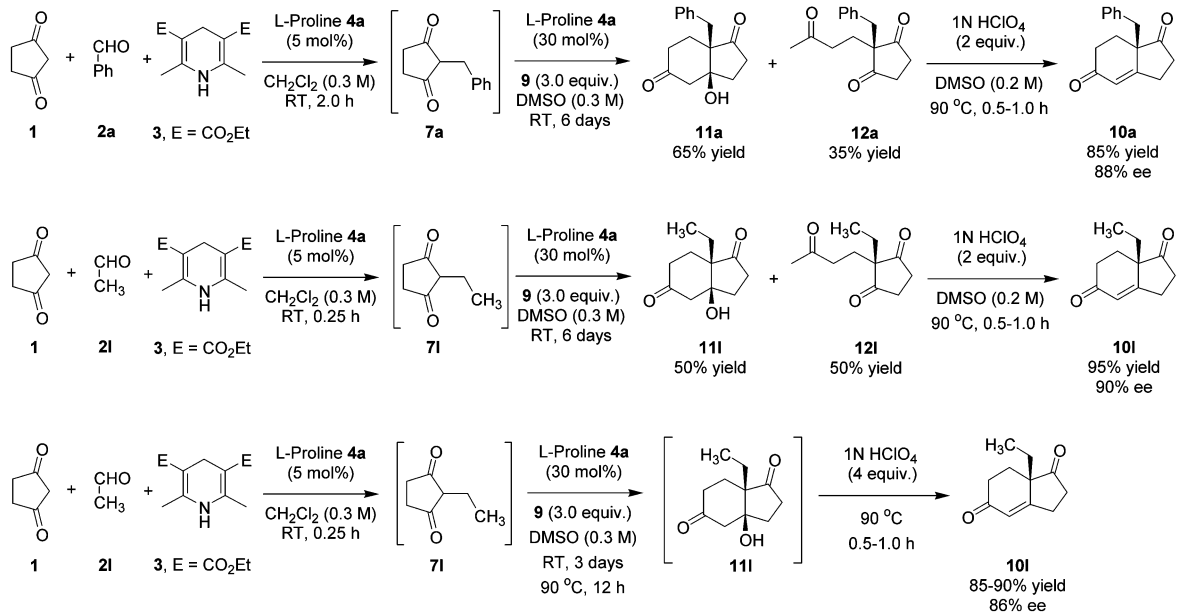
Fig. 2 Crystal structure of (+)-(*R*)-7*a*-benzyl-2,3,7,7*a*-tetrahydro-6*H*-indene-1,5-dione (**10a**).

1 N $HClO_4$ in DMSO at 90 °C for 1 h furnished the expected bicyclic-ketone (+)-**10a** in 85% yield with 91% ee as shown in Table 4, entry 2. D-Proline-catalyzed RA reaction of **7a** with **9** followed by hydrolysis furnished the opposite enantiomer of H–P ketone analogue (–)-**10a** in 96% yield with 90% ee (Table 4, entry 4). The absolute configuration of product (+)-**10a** prepared under L-proline-catalysis was established by using X-ray crystallography and also by comparison with the proline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction.[12] The crystal structure of product (+)-**10a** is depicted in Fig. 2.[10]

With an efficient amino acid-catalyzed asymmetric cascade RA protocol in hand, the scope of the proline-catalyzed cascade asymmetric RA reactions was investigated with various 2-alkyl-cyclopentane-1,3-diones **7** and methyl vinyl ketone **9**. A series of 2-alkyl-cyclopentane-1,3-diones **7a–n** were reacted with 3.0 equivalents of methyl vinyl ketone **9** catalyzed by 30 mol% of L-proline at 25 °C in DMSO for 6 days (Table 5). All expected bicyclic-alcohols of H–P ketone analogs **11a–n** were obtained in good yields, which on hydrolysis with 1 N $HClO_4$ in DMSO at 90 °C for 0.5–1 h furnished the expected bicyclic-ketones **10a–n** in good yields with 91–94% ee as shown in Table 5.

Amino acid-catalyzed asymmetric double cascade one-pot Robinson annulations

After successful demonstration of the amino acid-catalyzed cascade asymmetric O–H and RA reactions, we decided to investigate the combination of these two cascade reactions in one pot. Reaction of three equivalents of benzaldehyde **2a** with cyclopentane-1,3-dione **1** and Hantzsch ester **3** under 5 mol% of L-proline in CH_2Cl_2 at 25 °C for 2.0 h furnished the expected 2-benzyl-cyclopentane-1,3-dione **7a** in good yield. Removing the solvent CH_2Cl_2 by vacuum pump and adding DMSO solvent, 30 mol% of L-proline **4a** and freshly distilled methyl vinyl ketone **9** to the reaction mixture of cascade asymmetric O–H–RA furnished the expected bicyclic-alcohol of the H–P ketone analogue **11a** in 65% yield accompanied by Michael adduct **12a** in 35% yield as shown in Scheme 3. Hydrolysis of one-pot bicyclic-alcohol **11a** with 1 N $HClO_4$ in DMSO at 90 °C for 1 h furnished the expected bicyclic-ketone (+)-**10a** in 85% yield with 88% ee as shown in Scheme 3. Interestingly, in L-proline-catalyzed sequential one-pot double cascade asymmetric O–H–RA reactions, ee's were not effected by reaction by-product 2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester **8**. Successful combination of two



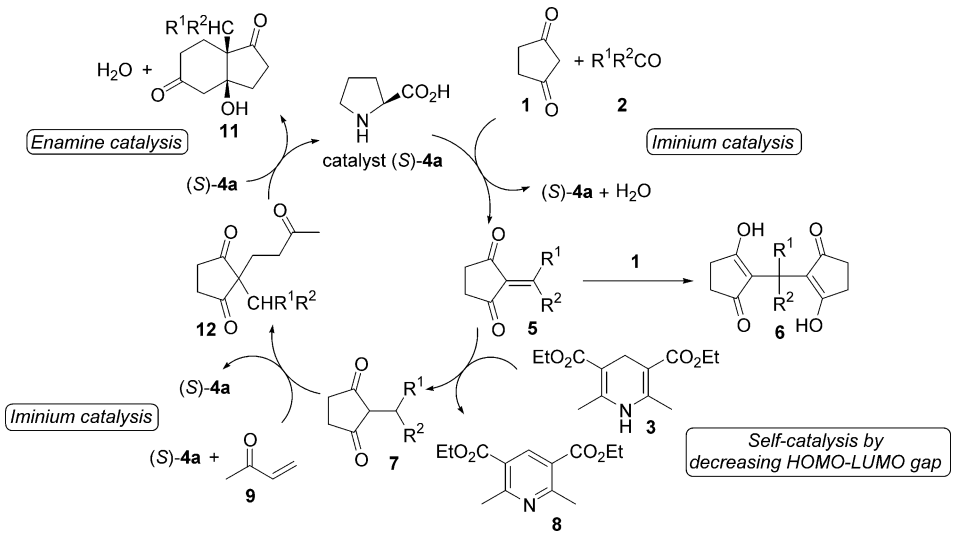
Scheme 3 Direct organocatalytic one-pot double cascade asymmetric synthesis of H–P ketone analogues **10**.

cascade O–H and RA reactions under L-proline-catalysis was demonstrated by one more example as shown in Scheme 3.

Even after 6 days at 25 °C, the double cascade asymmetric O–H–RA reaction of **1**, **2l**, **3** and **9** under **4a**-catalysis furnished the unreacted Michael adduct **12l** in 50% yield (see Scheme 3). For the complete conversion of Michael adduct **12l** into chiral bicyclic-alcohol **11l** in the double cascade reaction process, we performed the second step at 25 °C for 72 h and at 90 °C for 12 h followed by hydrolysis with 1 N $HClO_4$, furnishing the only expected H–P ketone analogue **10l** in 85–90% overall yield with 86% ee as shown in Scheme 3. Interestingly, there was only a 4% decrease in ee compared to the room temperature reaction and this one-pot double cascade synthetic strategy will have much impact on the asymmetric synthesis of functionalized small molecules.

Mechanistic insights

The most possible reaction mechanism for L-proline-catalyzed regio-, chemo- and enantio-selective synthesis of cascade products **7** and **10** through reaction of cyclopentane-1,3-dione **1**, aldehydes/ketones **2** and Hantzsch ester **3** is illustrated in Scheme 4. This catalytic sequential one-pot, double cascade is a four component reaction comprising a cyclopentane-1,3-dione **1**, aldehyde **2**, Hantzsch ester **3**, methyl vinyl ketone **9** and a simple chiral amino acid **4**, which is capable of catalyzing each step of this double cascade reaction. In the first step (Scheme 4), the catalyst (*S*)-**4** activates component **2** by, most likely, iminium ion formation, which then selectively adds to the cyclopentane-1,3-dione **1** *via* a Mannich and retro-Mannich type reaction to generate active



Scheme 4 Proposed catalytic cycle for the double cascade reactions.

olefin **5**.[4f] The following second step is biomimetic hydrogenation of active olefin **5** by Hantzsch ester **3** to produce **7** through self-catalysis by decreasing the HOMO–LUMO energy gap between **3** and **5** respectively.[4f–i] In the subsequent third step, Michael addition of **7** to methyl vinyl ketone **9** *via*, most likely, iminium ion activation leads to the formation of Michael adduct **12**.[12] In the fourth step, (*S*)-**4** catalyzed the asymmetric intramolecular aldol condensation of **12** *via* enamine catalysis[12] and returns the catalyst (*S*)-**4** for further cycles and releases the desired bicyclic-alcohol of H–P ketone analogue **11**.

Considering the recent applications of amino acid or amine-catalyzed olefination reactions[4a–i] and based on our recent discovery of reductive alkylation of CH-acids,[4a–i] we proposed that the most likely reaction course for the amino acid-catalyzed direct addition of cyclopentane-1,3-dione **1** to aldehydes **2** is the one outlined through iminium-catalysis as shown in Scheme 4. Formation of active olefins **5** through proline-catalysis by means of Mannich and retro-Mannich reactions supports our hypothesis that aldol products did not form in these reactions. This hypothesis is also supported by our recent discovery of organo-click reactions[4h] and the mechanistic investigation of pyrrolidine-catalyzed enal formation through aldehyde self-condensation reported by Saito *et al.*[13]

Highly chemoselective formation of cascade hydrogenated products **7** over bis-adduct **6** formation from reactants **1**, **3** and **5** can be explained by using HOMO–LUMO energy gaps and enthalpy differences as shown in Scheme 5. We have chosen **1**, **3** and **5a** for the model theoretical studies.[14] Self-catalyzed Michael reaction of cyclopentane-1,3-dione **1** with *in situ* generated active olefin **5a** furnishes the bis-adduct **6a**. For the same length of time, self-catalysis furnishes the hydrogenated product **7a** and pyridine **8** from hydride transfer reaction of Hantzsch ester **3** with *in situ* generated active olefin **5a**. Electronically and thermodynamically, the self-catalyzed hydride transfer reaction is more favorable than bis-adduct formation as revealed in Scheme 5.

In a first step to probe the competition between two self-catalyzed reactions between **1**, **3** and **5a**, we analyzed the energies of the HOMO and the LUMO for each compound involved in the reactions (Scheme 5). The calculated energy gaps between the LUMO of the active olefin **5a** and the HOMO of **1** are greater than the energy gaps between the LUMO of **5a** and the HOMO of the Hantzsch ester **3**. This result suggests that a self-catalyzed hydride transfer reaction proceeds faster than a Michael reaction of cyclopentane-1,3-dione **1** with active olefin **5a**, in agreement with the experimental results. Moreover, the energy gaps between the LUMO of **5a** and the HOMO of **1**/**3** agree with the experimental reactivity order, indicating that the hydride transfer is the rate-determining step and is a dynamically fast reaction compared to the Michael reaction. In a second step to probe the competition between two self-catalyzed reactions between **1**, **3** and **5a**, we analyzed the net heat of formations ($\Delta\Delta H$) of the two reactions (Scheme 5). The calculated heat of formation for the hydride transfer reaction is 7.823 kcal mol^{-1} more than the bis-adduct formation reaction as revealed in Scheme 5. This result also strongly suggests that a self-catalyzed hydride transfer reaction is thermodynamically a more favorable reaction than bis-adduct formation.

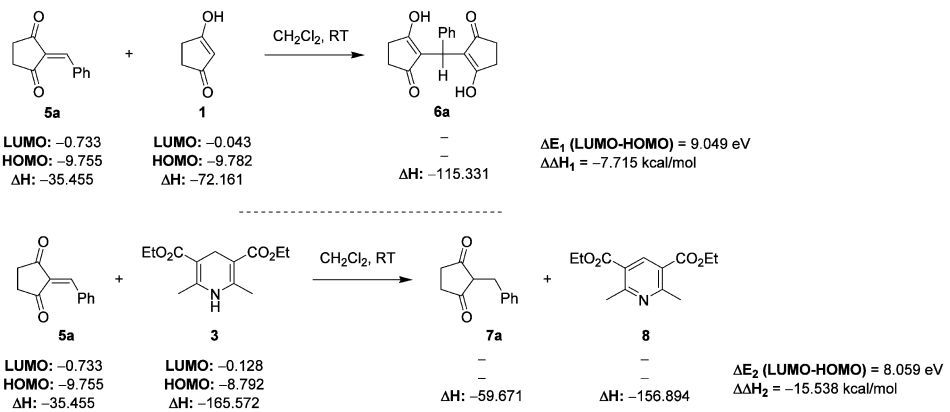
Conclusions

In summary, we have developed the metal-free double cascade synthesis of highly functionalized 2-alkyl-cyclopentane-1,3-diones **7**, chiral H–P ketone analogues **10** and 2-alkyl-3-methoxy-cyclopent-2-enones **13** from simple starting materials *via* cascade O–H, RA, O–H–RA and O–H–E reactions under amino acid-catalysis in one pot. For the first time, we have reported the reductive alkylation of highly reactive cyclopentane-1,3-dione **1** with aldehydes/ketones **2** and Hantzsch ester **3** under amino acid-catalysis. The reductive alkylation strategy, or cascade O–H reaction, proceeds in good yields with high chemo- and regio-selectivity using only 5 mol% of amino acid as the catalyst. In this article, we have demonstrated the concept of self-catalysis by decreasing the HOMO–LUMO energy gap between *in situ* generated olefins **5** and Hantzsch ester **3**. Furthermore, we have demonstrated the synthetic application of reductive alkylation products **7**. Further work is in progress to utilize novel O–H, O–H–E and O–H–RA reactions in synthetic chemistry.

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



Scheme 5 HOMO–LUMO energy gaps and enthalpy differences for self-catalyzed hydrogenation and bis-adduct formation reactions.

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 a VG7070 H mass spectrometer using the EI technique or a Shimadzu-LCMS-2010 A mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα ($\lambda = 0.71073$ Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube ($\lambda = 0.71073$ Å). 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 double cascade reactions

Amino acid-catalyzed cascade olefination–hydrogenation reactions with cyclopentane-1,3-dione. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **2**, 0.3 mmol of cyclopentane-1,3-dione **1** and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of solvent, and then the catalyst amino acid **4** (0.015 mmol, 5 mol%) was added 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 work-up, and pure cascade products **7** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Amino acid-catalyzed Robinson annulation reaction. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 2-alkyl-cyclopentane-1,3-diones **7** and 0.9 mmol of methyl vinyl ketone **9** was added 1.0 mL of DMSO solvent, and then the catalyst proline **4a** (0.09 mmol, 30 mol%) was added and the reaction mixture was stirred at 25 °C for 6 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 products **11** and **12** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Amino acid-catalyzed one-pot double cascade olefination–hydrogenation–Robinson annulation reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **2**, 0.3 mmol of cyclopentane-1,3-dione **1** and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of dichloromethane, and then the catalyst amino acid **4** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Scheme 3. After evaporation of the solvent completely, to the crude reaction mixture were added 0.9 mmol of methyl vinyl ketone **9**, 1.0 mL of DMSO solvent and 0.09 mmol of L-proline **4a** and the reaction mixture was stirred at 25 °C for 6 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 products **11** and **12** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

General procedure for the direct organocatalytic one-pot synthesis of 2-alkyl-3-methoxy-cyclopent-2-enones 13. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **2**, 0.3 mmol of cyclopentane-1,3-dione **1** and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of dichloromethane, and then the catalyst amino acid **4a** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Scheme 2. After evaporation of the solvent completely, to the crude reaction mixture was added an excess ethereal solution of diazomethane and the reaction mixture was stirred at room temperature for 0.5 h. After evaporation of the solvent and excess diazomethane completely in a fume hood, the crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure one-pot products **13** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

General procedure for dehydration of 7*a*-alkyl-3*a*-hydroxy-hexahydro-indene-1,5-diones 11. A solution of alcohol compound **11** (0.2 mmol) and 1 N $HClO_4$ (0.4 mmol) in DMSO (1.0 ml) was stirred at 90 °C for 0.5 to 1 h. After cooling, the reaction mixture was washed with water and the aqueous layer was extracted with dichloromethane (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).

Acknowledgements

This work was made possible by a grant from the Department of Science and Technology (DST), New Delhi. MK thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for his research fellowship. We thank Prof. M. V. Rajasekharan, Mr A. R. Biju and Dr P. Raghavaiah for their help in X-ray structural analysis.

References

1 For recent reviews on general cascade and multi-component reactions, see: (*a*) D. E. Cane, *Chem. Rev.*, 1990, **90**, 1089–1103; (*b*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136; (*c*) L. F. Tietze and A. Modi, *Med. Res. Rev.*, 2000, **20**, 304–322; (*d*) L. F. Tietze and F. Haunert, *Stimulating Concepts in Chemistry*, ed. F. Vogtle, J. F. Stoddart and M.Shibasaki, Wiley-VCH, Weinheim, 2000, pp. 39–64; (*e*) S. F. Mayer, W. Kroutil and K. Faber, *Chem. Soc. Rev.*, 2001, **30**, 332–339; (*f*) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun.*, 2003, 551–564; (*g*) J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001–1020; (*h*) D. J. Ramon and M. Yus, *Angew. Chem., Int. Ed.*,

2005, **44**, 1602–1634; (*i*) N. T. Patil and Y. Yamamoto, *Synlett*, 2007, 1994–2005; (*j*) D. M. D'Souza and T. J. J. Mueller, *Chem. Soc. Rev.*, 2007, **36**, 1095–1108.

2 For recent reviews on organocatalytic cascade and multi-component reactions, see: (*a*) H.-C. Guo and J.-A. Ma, *Angew. Chem., Int. Ed.*, 2006, **45**, 354–366; (*b*) H. Pellissier, *Tetrahedron*, 2006, **62**, 2143–2173; (*c*) C. J. Chapman and C. G. Frost, *Synthesis*, 2007, 1–21; (*d*) J. Gerencser, G. Dorman and F. Darvas, *QSAR Comb. Sci.*, 2006, **25**, 439–448; (*e*) G. Guillena, D. J. Ramon and M. Yus, *Tetrahedron: Asymmetry*, 2007, **18**, 693–700; (*f*) D. Enders, C. Grondal, Matthias and R. M. Huettl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–1581; (*g*) For an excellent review on iminium-ion induced cascade reactions, see: A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416–5470.

3 For recent reviews on organo-catalysis, see: (*a*) W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.*, 2004, **37**, 580–591; (*b*) B. List, *Acc. Chem. Res.*, 2004, **37**, 548–557; (*c*) A. Cordova, *Acc. Chem. Res.*, 2004, **37**, 102–112; (*d*) P. L. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138–5175; (*e*) A. Berkessel and H. Groger, *Asymmetric Organocatalysis*, WCH: Weinheim, Germany, 2004; (*f*) J. Seayed and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719–724; (*g*) E. R. Jarvo and J. M. Scott, *Tetrahedron*, 2002, **58**, 2481–2495; (*h*) B. List, *Tetrahedron*, 2002, **58**, 5573–5590; (*i*) B. List, *Synlett*, 2001, **11**, 1675–1686; (*j*) See also: B. List, *Acc. Chem. Res.*, 2004, **37**, number 8. Special edition devoted to asymmetric organocatalysis; (*k*) See also: B. List, *Chem. Rev.*, 2007, **107**, number 12. Special edition devoted to organocatalysis.

4 For recent papers on organocatalytic cascade and multi-component reactions from our group, see: (*a*) D. B. Ramachary, K. Ramakumar and M. Kishor, *Tetrahedron Lett.*, 2005, **46**, 7037–7042; (*b*) D. B. Ramachary, M. Kishor and K. Ramakumar, *Tetrahedron Lett.*, 2006, **47**, 651–656; (*c*) D. B. Ramachary, M. Kishor and G. Babul Reddy, *Org. Biomol. Chem.*, 2006, **4**, 1641–1646; (*d*) D. B. Ramachary and G. Babul Reddy, *Org. Biomol. Chem.*, 2006, **4**, 4463–4468; (*e*) D. B. Ramachary, K. Ramakumar and V. V. Narayana, *J. Org. Chem.*, 2007, **72**, 1458–1463; (*f*) D. B. Ramachary and M. Kishor, *J. Org. Chem.*, 2007, **72**, 5056–5068; (*g*) D. B. Ramachary, G. Babul Reddy and M. Rumpa, *Tetrahedron Lett.*, 2007, **48**, 7618–7623; (*h*) D. B. Ramachary, M. Kishor and Y. V. Reddy, *Eur. J. Org. Chem.*, 2008, 975–998; (*i*) D. B. Ramachary, Y. V. Reddy and B. V. Prakash, *Org. Biomol. Chem.*, 2008, **6**, 719–726. From other research groups, see: (*j*) D. B. Ramachary, N. S. Chowdari and C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2003, **42**, 4233–4237; (*k*) D. B. Ramachary, K. Anebouselvy, N. S. Chowdari and C. F. Barbas III, *J. Org. Chem.*, 2004, **69**, 5838–5849; (*l*) D. B. Ramachary and C. F. Barbas III, *Chem.–Eur. J.*, 2004, **10**, 5323–5331; (*m*) D. B. Ramachary and C. F. Barbas III, *Org. Lett.*, 2005, **7**, 1577–1580; (*n*) J. W. Yang, M. T. Hechavarria Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036–15037; (*o*) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051–15053; (*p*) M. Marigo, T. Schulte, J. Franzen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 15710–15711; (*q*) S. Brandau, E. Maerten and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 14986–14991; (*r*) D. Enders, M. R. M. Huettl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861–863; (*s*) D. Enders, M. R. M. Huettl, J. Runsink, G. Raabe and B. Wendt, *Angew. Chem., Int. Ed.*, 2007, **46**, 467–469; (*t*) G.-L. Zhao, W.-W. Liao and A. Cordova, *Tetrahedron Lett.*, 2006, **47**, 4929–4932; (*u*) R. Rios, H. Sunden, I. Ibrahem, G.-L. Zhao, L. Eriksson and A. Cordova, *Tetrahedron Lett.*, 2006, **47**, 8547–8551; (*v*) W. Wang, H. Li, J. Wang and L. Zu, *J. Am. Chem. Soc.*, 2006, **128**, 10354–10355.

5 For applications of Hajos–Parrish ketone analogues, see: (*a*) H. Smith, *J. Chem. Soc.*, 1964, 4472–4492; (*b*) G. Majetich, J. S. Song, C. Ringold, G. A. Nemeth and M. G. Newton, *J. Org. Chem.*, 1991, **56**, 3973–3988; (*c*) G. Majetich, J. S. Song, C. Ringold and G. A. Nemeth, *Tetrahedron Lett.*, 1990, **31**, 2239–2242; (*d*) G. A. Hughes and H. Smith, *U. S. Publ. Pat. Appl. B*, 1976, 57 pp, CODEN: USXXDP US 337823 19760323, CAN 85:192978 (patent written in English); (*e*) P. K. Ruprah, J.-P. Cros, J. E. Pease, W. G. Whittingham and J. M. J. Williams, *Eur. J. Org. Chem.*, 2002, 3145–3152; (*f*) L. Cao, J. Sun, X. Wang, R. Zhu, H. Shi and Y. Hu, *Tetrahedron*, 2007, **63**, 5036–5041; (*g*) H. Kasch and B. Liedtke, *U. S. Pat. Appl. Publ.*, 2006, 24 pp, CODEN: USXXCO US 2006089340 A1 20060427, CAN 144:433022 (patent written in English); (*h*) L. G. Sevillano, C. P. Melero, M. Boya, J. L. Lopez, F. Tome, E. Caballero, R. Carron, M. J. Montero, M. Medarde and A. San Feliciano, *Bioorg. Med. Chem.*, 1999, **7**, 2991–3001; (*i*) P. A. Grieco, N. Fukamiya and M. Miyashita, *J. Chem. Soc., Chem. Commun.*, 1976, 573–575; (*j*) S. Takano, K. Ogasawara, S. Sato and E. Goto, *Jpn. Kokai Tokkyo Koho*, 1987, 5 pp, CODEN: JKXXAF JP 62093286 A 19870428, CAN 108:37642 (patent written in Japanese); (*k*) S. Takano, S. Sato, E. Goto and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1986, 156–158; (*l*) R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott and P. A. Wehrli, *J. Org. Chem.*, 1975, **40**, 675–681.

6 For applications of 2-alkyl-cyclopentane-1,3-diones, see: (*a*) T. J. Norman, J. R. Porter, B. W. Hutchinson, A. J. Ratcliffe, J. C. Head, R. P. Alexander, B. J. Langham, G. J. Warrellow, S. C. Archibald and J. M. Linsley, *PCT Int. Appl.*, 2001, 91 pp, CODEN: PIXXD2 WO 2001079173 A2 20011025, CAN 135:331352 (patent written in English); (*b*) S. Ina, K. Yamana, K. Noda, T. Akiyama and A. Takahama, *Jpn. Kokai Tokkyo Koho*, 1999, 45 pp, CODEN: JKXXAF JP 11189577 A 19990713, CAN 131:87830 (patent written in Japanese); (*c*) S. Ina, K. Yamana and K. Noda, *Jpn. Kokai Tokkyo Koho*, 1998, 20 pp, CODEN: JKXXAF JP 10072415 A 19980317, CAN 128:257226 (patent written in Japanese); (*d*) M. S. Malamas, *U. S.*, 1995, 7 pp, CODEN: USXXAM US 5444086 A 19950822, CAN 124:29592 (patent written in English); (*e*) K. Nakano, T. Nakayachi, E. Yasumoto, S. R. Md, Morshed, K. Hashimoto, H. Kikuchi, H. Nishikawa, K. Sugiyama, O. Amano, M. Kawase and H. Sakagami, *Anticancer Res.*, 2004, **24**, 711–717; (*f*) S. Zhang, W. Luo, S. Zhang and X. Sun, *Ziran Zazhi*, 1987, **10**, 714–715; (*g*) J. Zhou, G. Lin and Q. Sun, *Huaxue Shijie*, 1986, **27**, 490–493; (*h*) E. Lee, S. Y. Koh, B. D. Song and T. K. Park, *Bull. Korean Chem. Soc.*, 1984, **5**, 223–226; (*i*) S. Sarshar, *PCT Int. Appl.*, 2005, 69 pp, CODEN: PIXXD2 WO 2005108338 A1 20051117, CAN 143:477744 (patent written in English); (*j*) A. S. R. Anjaneyulu, M. V. R. K. Murthy, P. M. Gowri, M. J. R. V. Venugopal and H. Laatsch, *J. Nat. Prod.*, 2000, **63**, 1425–1426; (*k*) A. Schmidt and W. Boland, *J. Org. Chem.*, 2007, **72**, 1699–1706; for the applications of 2-alkyl-3-methoxy-cyclopent-2-enones, see: (*l*) G. A. Tolstikov, S. A. Ismailov, Y. L. Vel'der and M. S. Miftakhov, *Zhurnal Organicheskoi Khimii*, 1991, **27**, 83–90; (*m*) G. L. Nelson, *U. S.*, 1982, 7 pp, CODEN: USXXAM US 4338466 A 19820706, CAN 98:16495 (patent written in English); (*n*) H. Schick, M. Henning, H. P. Welzel and S. Schwarz, *Ger. (East)*, 1979, 8 pp, CODEN: GEXXA8 DD 138767 19791121, CAN 93:71116 (patent written in German); (*o*) P. Aujla, T. J. Norman, J. R. Porter, S. Bailey and S. Brand, *PCT Int. Appl.*, 2003, 97 pp, CODEN: PIXXD2 WO 2003011815 A1 20030213, CAN 138:137592 (patent written in English); (*p*) F. A. Lakhvich, F. S. Pashkovskii and L. G. Lis, *Seryya Khimichnykh Navuk*, 1987, 53–59; (*q*) H. Liang, A. Schule, J.-P. Vors and M. A. Ciufolini, *Org. Lett.*, 2007, **9**, 4119–4122.

7 (*a*) M. Bassetti, G. Cerichelli and B. Floris, *Gazz. Chim. Ital.*, 1986, **116**, 583–585. For the two-step synthesis of 2-alkyl-cyclopentane-1,3-diones, see: (*b*) K. Hiraga, *Chem. Pharm. Bull.*, 1965, **13**, 1359–1361; (*c*) K. Takeishi, K. Sugishima, K. Sasaki and K. Tanaka, *Chem.–Eur. J.*, 2004, **10**, 5681–5688; (*d*) F. Gao and D. J. Burnell, *J. Org. Chem.*, 2006, **71**, 356–359; (*e*) L. Novak, G. Baan, J. Marosfalvi and C. Szantay, *Chem. Ber.*, 1980, **113**, 2939–2949; (*f*) L. Novak, G. Baan, J. Marosfalvi and C. Szantay, *Tetrahedron Lett.*, 1978, 487–490; (*g*) F. S. Pashkovsky, I. P. Lokot and F. A. Lakhvich, *Synlett*, 2001, 1391–1394; (*h*) A. A. Akhrem, F. A. Lakhvich, L. G. Lis, V. A. Khripach, N. A. Fil'chenkov, V. A. Kozinets and F. S. Pashkovskii, *Dokl. Akad. Nauk SSSR*, 1990, **311**, 1381–1384; (*i*) R. Bucourt, A. Pierdet, G. Costerousse, D. Hainaut, R. Joly, J. Warnant and B. Goffinet, *U. S.*, 1970, 5 pp, CODEN: USXXAM US 3518296 19700630, CAN 73:66128 (patent written in English); (*j*) K. Shimizu and F. Matsushita, *PCT Int. Appl.*, 2007, 99 pp, CODEN: PIXXD2 WO 2007004442 A1 20070111, CAN 146:142304 (patent written in Japanese); (*k*) A. M. Cohen, *Ger. Offen.*, 1971, 8 pp, CODEN: GWXXBX DE 2059889 19710624, CAN 75:63238 (patent written in German); (*l*) K. Matoba, M. Tachi, T. Itooka and T. Yamazaki, *Chem. Pharm. Bull.*, 1986, **34**, 2007–2012; (*m*) K. Fuchs and L. A. Paquette, *J. Org. Chem.*, 1994, **59**, 528–532; (*n*) D. Lertpibulpanya and S. P. Marsden, *Org. Biomol. Chem.*, 2006, **4**, 3498–3504.

8 J. R. Dimmock, S. K. Raghavan and G. E. Bigam, *Eur. J. Med. Chem.*, 1988, **23**, 111–117.

9 (*a*) P. E. Eaton, W. H. Bunnelle and P. Engel, *Can. J. Chem.*, 1984, **62**, 2612–2626; (*b*) P. E. Eaton and W. H. Bunnelle, *Tetrahedron Lett.*, 1984, **25**, 23–26; (*c*) W. A. Herrmann, *Ger. Offen.*, 1991, 6 pp, CODEN: GWXXBX DE 4101737 A1 19910801, CAN 115:158156 (patent written in German); (*d*) M. L. Bolte, W. D. Crow and S. Yoshida, *Aust. J. Chem.*, 1982, **35**, 1421–1429; (*e*) M. L. Bolte, W. D. Crow and S. Yoshida, *Aust. J. Chem.*, 1982, **35**, 1411–1419; (*f*) W. H. Bunnelle and L. A. Meyer, *J. Org. Chem.*, 1988, **53**, 4038–4042.

10 CCDC-674004 for **7i** and CCDC-674005 for **10a** contain the supplementary crystallographic data for this paper. These 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 mailto:deposit@ccdc.cam.ac.uk.
11 (*a*) C. F. Thompson, N. Quraishi, A. Ali, R. T. Mosley, J. R. Tata, M. L. Hammond, J. M. Balkovec, M. Einstein, L. Ge, G. Harris, T. M. Kelly, P. Mazur, S. Pandit, J. Santoro, A. Sitlani, C. Wang, J. Williamson, D. K. Miller, T. D. Yamin, C. M. Thompson, E. A. O'Neill, D. Zaller, M. J. Forrest, E. Carballo-Jane and S. Luell, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3354–3361; (*b*) C. J. Smith, A. Ali, J. M. Balkovec, D. W. Graham, M. L. Hammond, G. F. Patel, G. P. Rouen, S. K. Smith, J. R. Tata, M. Einstein, L. Ge, G. S. Harris, T. M. Kelly, P. Mazur, C. M. Thompson, C. F. Wang, J. M. Williamson, D. K. Miller, S. Pandit, J. C. Santoro, A. Sitlani, T. D. Yamin, E. A. O'Neill, D. M. Zaller, E. Carballo-Jane, M. J. Forrest and S. Luell, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2926–2931.
12 (*a*) Z. G. Hajos and D. R. Parrish, *Ger. Offen.*, 1971, CODEN: GWXXBX DE 2102623 19710729, CAN 76:59072, (in German: 42 pp); (*b*) U. Eder, R. Wiechert and G. Sauer, *Ger. Offen.*, 1971, CODEN: GWXXBX DE 2014757 19711007, CAN 76:14180 (in German: 20 pp); (*c*) G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky and C. F. Barbas III, *J. Am. Chem. Soc.*, 1997, **119**, 8131–8132; (*d*) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 11273–11283; (*e*) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 12911–12912; (*f*) L. Hoang, S. Bahmanyar, K. N. Houk and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 16–17; (*g*) S. Bahmanyar, K. N. Houk, H. J. Martin and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 2475–2479; (*h*) B. List, L. Hoang and H. J. Martin, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5839–5842; (*i*) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong and K. N. Houk, *Acc. Chem. Res.*, 2004, **37**, 558–569; (*j*) P. H.-Y. Cheong and K. N. Houk, *Synthesis*, 2005, 1533–1537.
13 (*a*) B. List and C. Castello, *Synlett*, 2001, **11**, 1687–1689; (*b*) T. Ishikawa, E. Uedo, S. Okada and S. Saito, *Synlett*, 1999, **4**, 450–452; (*c*) R. Tanikaga, N. Konya, K. Hamamura and A. Kaji, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3211–3216.
14 HOMO–LUMO energies, heat of formations (ΔH) of compounds **5a**, **1**, **6a**, **3**, **7a** and **8** are calculated based on PM3 (MOPAC) calculations in *CS Chem3D Ultra* using wave function as closed shell (restricted) and minimizing the energy to a minimum RMS gradient of 0.100.