Rapid two-step synthesis of drug-like polycyclic substances by sequential multi-catalysis cascade reactions†

Dhevalapally B. Ramachary,* Rumpa Mondal and Chintalapudi Venkaiah

Received 28th September 2009, Accepted 19th October 2009
First published as an Advance Article on the web 28th October 2009
DOI: 10.1039/b920152a

An efficient amino acid-/self-/base-/ruthenium-/thermal-catalyzed two-step process for the synthesis of functionalized drug-like carbocycles was achieved through combinations of cascade TCRA/*C*-allylation/enyne-RCM/Diels–Alder reactions as key steps starting from simple acyclic substrates. In this communication, we report the two-step synthesis of drug-like carbocycles through a combination of organocatalysis with ruthenium-catalysis.

Highly functionalized drug-like carbocycles are of considerable importance in the pharmaceutical industry.[1] As such, the development of new and more general green one-pot cascade methods for their preparation is of significant interest for the development of new drugs.[2a–i] Especially, functionalized polycyclic carbocycles have attracted considerable attention as a result of their structural complexity, biological activity and their presence in a variety of natural and unnatural products.[2j–l] Thus, the diversity-oriented synthesis of polycyclic carbocycles represents an important task because of the synthetic challenge, and also widespread occurrence of such structural motifs and their use as building blocks. Herein, we report the multi-catalytic cascade approach to the high-yielding synthesis of functionalized drug-like carbocycles from a two-step sequence *via* a "combination of amino acid-/self-/base-/ruthenium-/thermal-catalysis".

Recently olefin metathesis of dienes and enynes catalyzed by Grubbs' catalysts provided a general platform to a variety of carbocycles with good yields.[3] The manifestation of olefin metathesis technology triggered a burst of activity in the synthesis of a huge variety of differently substituted carbocycles. Reactions performed in a sequential cascade approach can generate the desired targets efficiently in a single reaction vessel without the need to purify at each step. A particularly attractive green cascade process occurs when two or more sequential cascade reactions are triggered by more than two catalysts in one-pot. The catalytic ability and orthogonal catalysis of L-proline to function as a soft catalyst for the cascade three-component reductive alkylation (TCRA) reactions has led to several examples, where combination of this TCRA with other transformations in one-pot provided efficient new entries into useful drug intermediates.[4a–i]

During our studies on amino acid-/self-catalyzed cascade TCRA reactions,[4a–i] we noted that functionalized 2-ethynyl-benzaldehydes **1** can serve as suitable starting materials for the generation of drug-like carbocycles **11** and **12** *via* combination of TCRA, *C*-allylation (*C*-A), enyne-ring closing metathesis (enyne-RCM) and Diels–Alder (DA) reactions as key processes (Scheme 1).

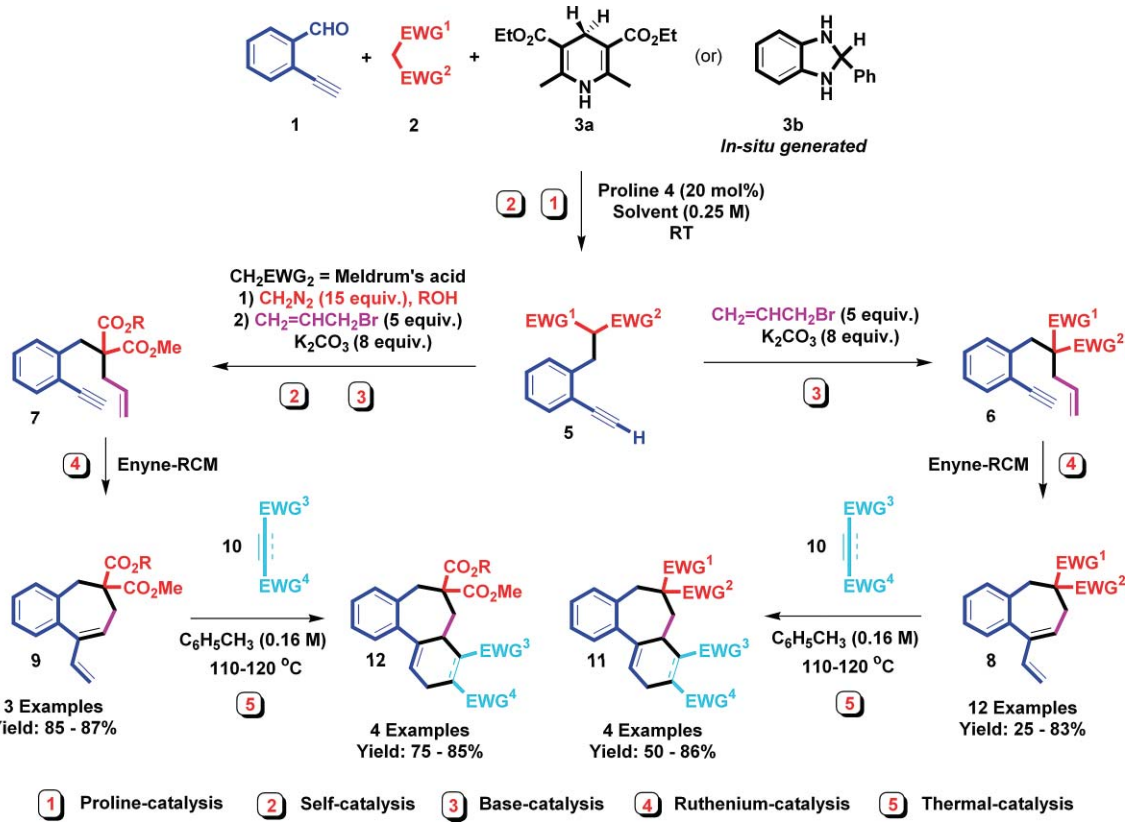
Herein, we discovered a novel and green technology for the two-step synthesis of highly substituted drug-like carbocycles **11** and **12** using proline-/self-/potassium carbonate-/ruthenium-/thermal-catalysis through cascade TCRA, *C*-A, enyne-RCM and DA reactions as key steps starting from commercially available 2-ethynyl-benzaldehydes **1**, CH-acids **2**, organic-hydrides **3**, allyl bromide, diazomethane, reactive dienophiles **10**, L-proline **4**, K_2CO_3 and Grubbs' 1st or 2nd generated ruthenium catalysts, an approach we call the "multi-catalysis cascade (MCC) approach to carbocycles" (Scheme 1).[4a–o] In this communication, we report a new synthetic strategy by the combination of organocatalysis with enyne-RCM/DA reactions to deliver complex carbocycles.

We found that the amino acid L-proline **4** readily catalyzes the olefination of **1a** with ethyl cyanoacetate **2a** to furnish the active olefin, which on *in situ* treatment with Hantzsch ester **3a** produced the TCRA product **5aa** with very good conversion in EtOH or DMSO at 25 °C for 1 h, which on treatment with allyl bromide and K_2CO_3 at 25 °C for 11 h furnished the ene-yne product **6aa** with 95% yield (result not shown in Table 1). The same sequential cascade TCRA/*C*-A reaction with *in situ* generated hydride source, 2-phenyl-2,3-dihydro-1*H*-benzoimidazole **3b** also furnished the product **6aa** with 93% yield (Table 1, entry 1). The optimum conditions involved the use of 20 mol% catalyst **4** and 8 equiv. of K_2CO_3 in cascade TCRA/*C*-A reaction of **1a**, **2a**, **3a**/**3b** and allyl bromide in EtOH or DMSO at 25 °C to furnish **6aa** in very good yield.

With the optimized reaction conditions in hand, the scope of the sequential one-pot cascade TCRA/*C*-A reactions was investigated. A variety of CH-acids **2a–l** were reacted with 1 equiv. of 2-ethynyl-benzaldehyde **1a**, 1 equiv. of organic hydride **3a**/**3b** and 5 equiv. of allyl bromide under the sequential catalysis by 20 mol% of L-proline-/self and K_2CO_3 in DMSO at 25 °C for 0.75 to 24 h (Table 1). Acyclic and cyclic CH-acids **2a–l** generated the expected ene-yne products **6** with excellent yields (Table 1). Reaction of (1*R*,2*S*,5*R*)-cyano-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester **2f** with **1a**, **3b** and allyl bromide under L-proline-/self-/K_2CO_3-catalysis furnished the product (–)-**6af**, but unfortunately we observed only 1 : 1 dr (Table 1, entry 6). Reaction of Meldrum's acid **2h** with **1a**, **3a** and allyl bromide under L-proline-/self-/K_2CO_3-catalysis furnished the product **6ah** in 76% yield (Table 1, entry 8). In a similar manner, ene-yne compound **6ai** was furnished as the major product with 60% yield (Table 1, entry 12). Interestingly, reaction of cyclic CH-acids **2j–l**

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. See DOI: 10.1039/b920152a



Scheme 1 Synthesis of drug-like carbocycles *via* a two-step sequence.

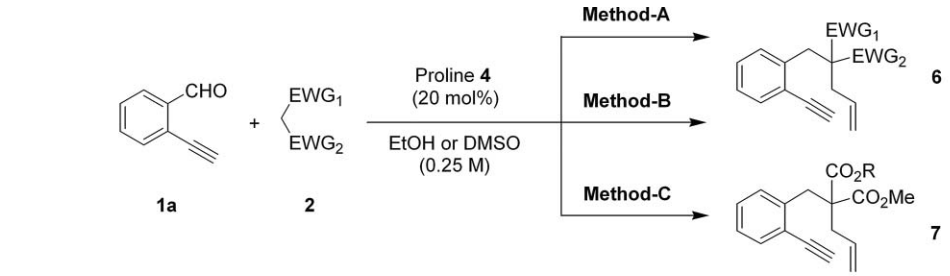
with **1a**, **3a** and allyl bromide under L-proline-/self-/K_2CO_3-catalysis furnished the ene-yne compounds **6aj–al** as major products in 50-65% yields with accompanying by TCRA/*O*-A by-products **13aj–al** in 25-50% yields as shown in Table 1, entries 13-15. This may be due to the highly acidic nature of cyclic CH-acids **2j–l** compared to acyclic CH-acids **2a–g** in the compounds **5aj–al**. By-products **13aj–al** can be converted into required ene-yne compounds **6aj–al** by thermal-catalysis through Claisen rearrangement and by-product **13al** was transformed into ene-yne **6al** in 75% yield after heating at 120 °C for 23 h in toluene (eq S1, see Supporting Information†). Structure of products **6aa–al** was confirmed by NMR and mass analysis.

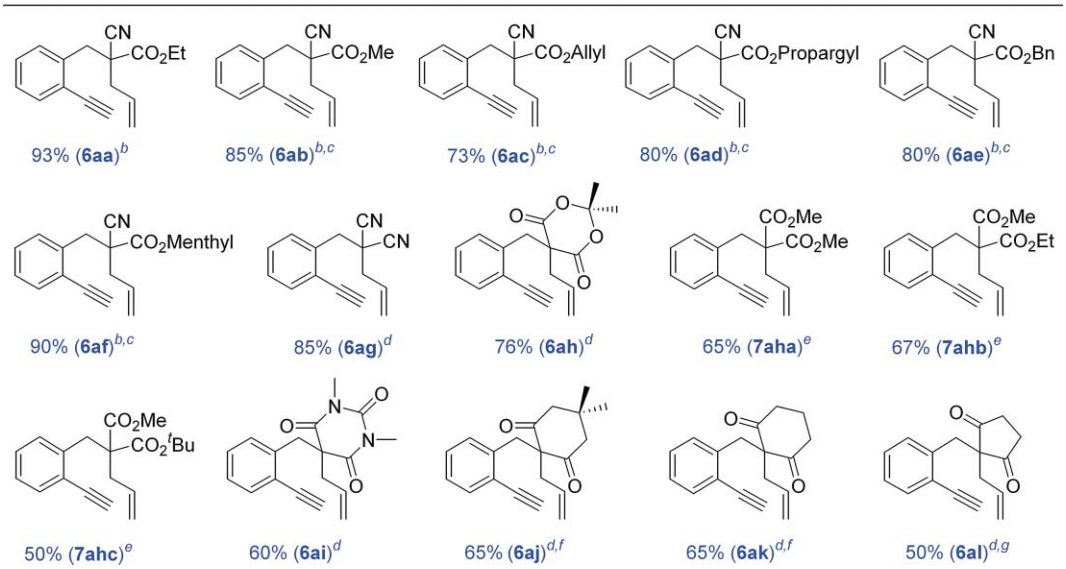
For the synthesis of ene-ynes **7aha–ahc** containing malonates, we utilized the *in situ* generation and esterfication of methoxycarbonylketenes with alcohols *via* the sequential MCC one-pot TCRA-/alkylation-/ketenization-/esterification (TCRA/A/K/E) followed by *C*-allylation (*C*-A) reactions of 2-ethynyl-benzaldehyde **1a**, Meldrum's acid **2h**, Hantzsch ester **3a**, diazomethane, alcohols **a–c** and allyl bromide *via* iminium-/self-/self-/self-/self-/base-catalysis in one-pot.[4i] Interestingly, L-proline-/self-catalyzed cascade TCRA reaction of Meldrum's acid **2h** and 2-ethynyl-benzaldehyde **1a** with organic-hydride **3a** in MeOH **a** at 25 °C for 1 h furnished the expected TCRA product **5ah** in >99% conversion, which on *in situ* treatment with ethereal diazomethane at 0 °C → 25 °C for 2 h furnished the expected dimethyl-2-(2-ethynyl-benzyl)-malonate **5′aha** with 99% conversion, which on *in situ* treatment with allyl bromide and K_2CO_3 furnished the expected ene-yne compound **7aha** in 65% yield (Table 1, entry 9). In a similar manner, we synthesized two more ene-ynes **7ahb–ahc** with good yields by performing the sequential MCC reactions of TCRA/A/K/E/*C*-A reactions in ethanol **b** and *t*-butanol **c** solvents respectively as shown in Table 1, entries 10 and 11.

With the ene-yne library in hand, first we focused on the optimization of enyne-RCM reaction on **6aa** by changing reactions conditions as shown in Table 2. Interestingly, enyne-RCM reaction of **6aa** using Grubbs' 1st generation catalyst in CH_2Cl_2 at 25 °C for 14 h furnished the highly functionalized benzocycloheptene **8aa** in 55% yield; but the same reaction with Grubbs' 2nd generation catalyst also furnished the **8aa** in 55% yield (Table 2, entries 1 and 2). Enyne-RCM reaction of **6aa** with Hoveyda–Grubbs' 1st generation catalyst in CH_2Cl_2 at 25 °C for 11 h is not superior as compared to Grubbs' 1st generation catalyst (Table 2, entry 3). Surprisingly, it was observed that no products were formed employing enyne-RCM reaction of **6aa** with $PtCl_2$ in $C_6H_5CH_3$ at 25/85 °C for 21 h as shown in Table 2, entries 7 and 8.[2f] Interestingly, enyne-RCM reaction of **6aa** using Grubbs' 1st generation catalyst in CH_2Cl_2 at 45 °C for 5 h furnished the benzocycloheptene **8aa** in 63% yield; but the same reaction at similar conditions with Grubbs' 2nd generation catalyst furnished the **8aa** with only 59% yield (Table 2, entries 4 and 6). The optimum conditions involved the use of 5 mol% Grubbs' 1st generation catalyst in enyne-RCM reaction of **6aa** in CH_2Cl_2 at 45 °C for 5 h to furnish **8aa** with good yield.

With the optimized reaction conditions in hand, the scope of the ruthenium-catalyzed enyne-RCM reactions was investigated

Table 1 Sequential multi-catalysis cascade approach to the ene-ynes **6/7**[a]



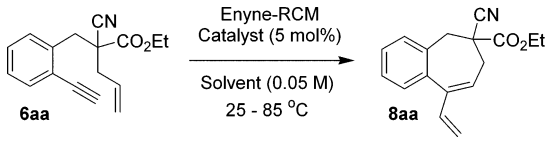


[a] Yield refers to the column purified products. [b] Reagents and conditions for **Method-A**: A mixture of **1a** (0.3 mmol), **2** (0.3 mmol) and proline **4** (20 mol%) in EtOH (0.25 M) was stirred at room temperature for 0.5–11 h. Then *o*-phenylenediamine (0.3 mmol) and PhCHO (0.3 mmol) were added and stirring was continued at the same temperature for 1.5–16 h. Then solvent was evaporated and CH_2=$CHCH_2Br$ (5 equiv.), K_2CO_3 (8 equiv.) and DMSO (0.25 M) were added and stirring was continued at the same temperature for 0.25–11 h. [c] DMSO was used as solvent throughout the reaction sequence. [d] Reagents and conditions for **Method-B:** A mixture of **1a** (0.3 mmol), **2** (0.3 mmol), **3a** (0.3 mmol) and proline **4** (20 mol%) in EtOH (0.25 M) was stirred at room temperature for 0.75–24 h. Then solvent was evaporated and CH_2=$CHCH_2Br$ (5 equiv.), K_2CO_3 (8 equiv.) and DMSO (0.25 M) were added and stirring was continued at the same temperature for 0.5–1 h. [e] Reagents and conditions for **Method-C:** All reactants **1a**, **2h**, **3a** and catalyst **4** were mixed at the same time in R-OH **a–c** and stirred at 25 °C, then 15 equiv. of ethereal diazomethane was added and stirred at 25 °C for 2–6 h. Then solvent was evaporated and CH_2=$CHCH_2Br$ (5 equiv.), K_2CO_3 (6 equiv.) and DMSO (0.25 M) were added and stirring was continued at the same temperature for 12 h. [f] 25–30% of *O*-allylated (*O*-A) products **13aj** or **13ak** are formed. [g] 50% of *O*-allylated (*O*-A) product **13al** is formed.

with a variety of functionalized ene-ynes **6/7** as shown in Table 3. A series of ene-ynes **6** were converted into benzocycloheptenes **8aa–al** in moderate to good yields as shown in Table 3. Interestingly, enyne-RCM reaction of diene-yne **6ac** using Grubbs' 1st generation catalyst (5 mol%) in CH_2Cl_2 at 45 °C for 5 h furnished the chemoselective product **8ac** in 50-60% conversion and 25% yield (Table 3, entry 3). In a similar manner, selective enyne-RCM of ene-diyne **6ad** using Grubbs' 1st generation catalyst (5 mol%) in CH_2Cl_2 at 45 °C for 8 h furnished the chemoselective product **8ad** in 50-60% conversion and 25% yield (Table 3, entry 4). Enyne-RCM reaction of 1 : 1 dr mixture of chiral (–)-**6af** furnished the expected benzocycloheptene (–)-**8af** in 66% yield with 1 : 1 dr mixture as shown in Table 3, entry 6. Unfortunately, enyne-RCM reaction on Meldrum's acid containing ene-yne **6ah** didn't give the expected product **8ah** even after testing at two different conditions as shown in Table 3, but the similar reaction on barbituric acid containing ene-yne **6ai** furnished the expected spiro-benzocycloheptene **8ai** in moderate yield as shown in Table 3. Enyne-RCM reaction of cyclic ene-ynes **6aj–al** using Grubbs' 1st generation catalyst (5 mol%) in CH_2Cl_2 at 45 °C for 5 h furnished the spiro-products **8aj–al** in 70-83% yields (Table 3, entries 13–15).

For the rapid high-yielding one-pot synthesis of complex drug-like molecules and with synthetic/pharmaceutical applications in mind, we extended the application of amino acid-/self-/K_2CO_3-/[Ru]-promoted cascade TCRA/*C*-A/enyne-RCM products **8aa–al** into a novel highly substituted polycyclic substances **11** and **12** through TCRA/*C*-A/enyne-RCM/DA reaction sequence (Table 4). Simple acyclic substance, 2-ethynyl-benzaldehyde **1a** was converted into highly functionalized spiro-polycyclic *endo*-product **11aja** with >99% de in stereoselective manner with 55.9% overall yield through a sequence of amino acid-/self-/K_2CO_3-catalyzed cascade TCRA/*C*-A, ruthenium-promoted enyne-RCM followed by heat-promoted Diels–Alder (DA)

Table 2 Optimization for enyne-RCM reaction



Entry	Catalyst (5 mol%)	Solvent (0.05 M)	T/°C	Time/h	Yield (%)[a]
1	Grubbs' 1st generation	CH_2Cl_2	25	14	55
2	Grubbs' 2nd generation	CH_2Cl_2	25	11	55
3[b]	Hoveyda–Grubbs' 1st generation	CH_2Cl_2	25	11	34
4	Grubbs' 1st generation	CH_2Cl_2	45	5	63
5[b]	Grubbs '1st generation	$PhCH_3$	85	2	45
6	Grubbs' 2nd generation	CH_2Cl_2	45	7	59
7[c]	$PtCl_2$	$PhCH_3$	25	21	—
8[d]	$PtCl_2$	$PhCH_3$	85	21	—

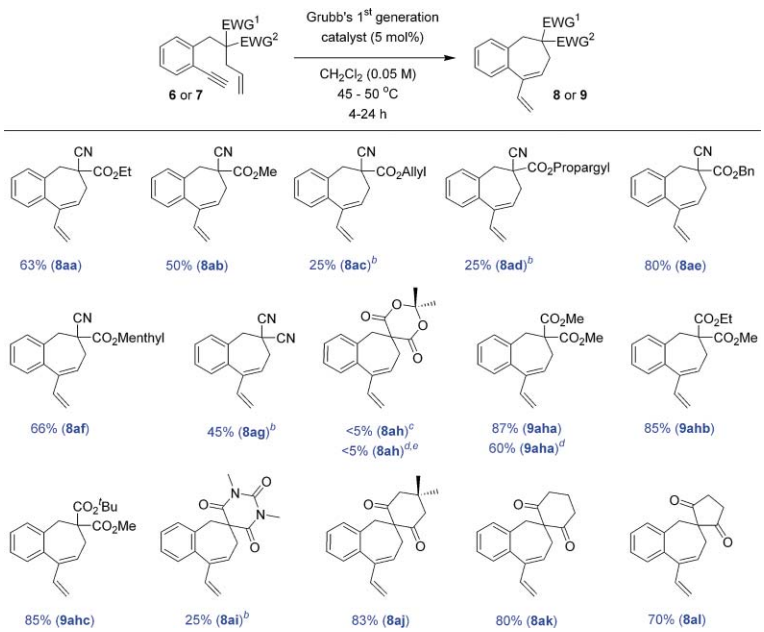
[a] Yield refers to the column purified products. [b] Reaction conversion is only 50–60%. [c] Ene-yne **6aa** is recovered. [d] Starting material **6aa** is decomposed.

reaction with 1-phenyl-pyrrole-2,5-dione **10a** in one-pot as shown in Table 4, entry 1. Generality of the amino acid-/self-/K_2CO_3-/[Ru]-/heat-catalyzed stereoselective sequential one-pot cascade TCRA/*C*-A or TCRA/A/K/E/*C*-A, enyne-RCM and DA reactions was further confirmed by four more examples using different CH-acids **2** and dienophile **10a** to furnish the expected highly functionalized polycyclic *endo*-product **11aka** in 32.5% overall yield with >99% de, *endo*-product **11ala** in 25.0% overall yield with >99% de, *endo*-product **12aha**$_2$ in 48.75% overall yield with >99% de, and *endo*-product **12ahba** in 57.0% overall yield with ≤5% de, respectively as shown in Table 4. Structure and stereochemistry of polycyclic substances **11**–**12** were confirmed by NMR analysis and also by mass analysis. For the pharmaceutical applications, a diversity-oriented library of polycyclic substances **11**/**12** could be generated by using our two-step sequential MCC reactions.

In a similar manner, 2-ethynyl-benzaldehyde **1a** was converted into highly functionalized spiro tetra-cyclic product **11ajb** in stereospecific manner with 42% overall yield through a sequence of amino acid-/self-/K_2CO_3-catalyzed cascade TCRA/*C*-A, [Ru]-promoted enyne-RCM followed by heat-promoted Diels–Alder reaction with diethyl acetylenedicarboxylate **10b** in one-pot as shown in Table 4, entry 4 and generality of this two-step sequential MCC reactions was further confirmed by two more examples using different CH-acids **2** and dienophile **10b** to furnish the expected highly functionalized tri-cyclic *endo*-product **12ahab** in 54.0% overall yield with >99% de and *endo*-product **12ahb**$_2$ in 57% overall yield with ≤5% de, respectively as shown in Table 4, entries 7 and 8. This two-step sequential MCC method will be showing much impact on the high-yielding synthesis of functionalized carbocycles.

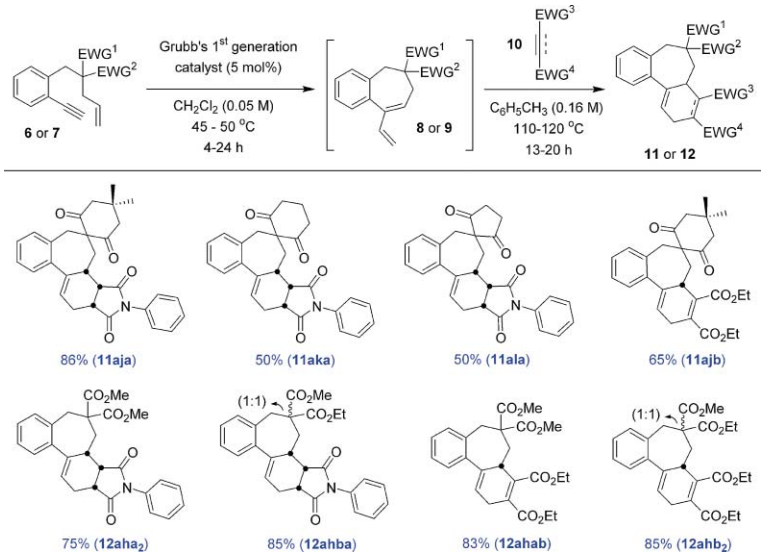
In summary, we have developed the two-step sequential MCC chemistry for the synthesis of highly substituted drug-like carbocycles **8**, **9**, **11** and **12** from simple starting materials *via* TCRA/*C*-A, TCRA/A/K/E/*C*-A, enyne-RCM and Diels–Alder reactions. The MCC strategy proceeds in good yields with high selectivity using proline-/self-/K_2CO_3-/[Ru]-/heat as the catalysts. Further work is in progress to utilize novel MCC reactions in synthetic organic chemistry.

Table 3 Synthesis of enyne-RCM products **8**/**9**[a]



[a] Yield refers to the column purified products. [b] Reaction conversion is only 50–60%. [c] Ene-yne **6ah** is recovered. [d] Reaction conditions: $PtCl_2$ (5 mol%), $C_6H_5CH_3$ (0.05 M), 110 °C, 5 h. [e] Starting material **6ah** is decomposed.

Table 4 Rapid one-pot assembly of drug-like polycyclic substances **11/12** from simple acyclic molecules[a]



[a] Yield refers to the column purified products.

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]. RM and CV thank CSIR (New Delhi) for their research fellowships.

Notes and references

1 (*a*) G. Schneider and U. Fechner, *Nat. Rev. Drug Discovery*, 2005, **4**, 649–663; (*b*) R. J. Zauhar, G. Moyna, L. Tian, Z. Li and W. J. Welsh, *J. Med. Chem.*, 2003, **46**, 5674–5690; (*c*) P. Gribbon and A. Sewing, *Drug Discovery Today*, 2005, **10**, 17–22; (*d*) T. Honma, *Med. Res. Rev.*, 2003, **23**, 606–632; (*e*) N. Yoshihiko and I. Akiko, *Tetrahedron*, 1991, **47**, 8985–8990; (*f*) D. Bailey and D. Brown, *Drug Discovery Today*, 2001, **6**, 57–59; (*g*) R. S. Bohacek, C. McMartin and W. C. Guida, *Med. Res. Rev.*, 1996, **16**, 3–50.

2 (*a*) B. M. Trost and M. Lautens, *J. Am. Chem. Soc.*, 1985, **107**, 1781–1783; (*b*) S. Ma and E.-I. Negishi, *J. Org. Chem.*, 1994, **59**, 4730–4732; (*c*) B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan and D. T. MacPherson, *J. Am. Chem. Soc.*, 1994, **116**, 4255–4267; (*d*) S. Ma and E.-I. Negishi, *J. Am. Chem. Soc.*, 1995, **117**, 6345–6357; (*e*) Y. Yamamoto, Y. Nakagai, N. Ohkoshi and K. Itoh, *J. Am. Chem. Soc.*, 2001, **123**, 6372–6380; (*f*) A. M. Echavarren and C. Nevado, *Chem. Soc. Rev.*, 2004, **33**, 431–436; (*g*) B. L. Ashfeld, K. A. Miller, A. J. Smith, K. Tran and S. F. Martin, *J. Org. Chem.*, 2007, **72**, 9018–9031; (*h*) F.-X. Felpin and E. Fouquet, *ChemSusChem*, 2008, **1**, 718–724; (*i*) C. Kammerer, G. Prestat, T. Gaillard, D. Madec and G. Poli, *Org. Lett.*, 2008, **10**, 405–408; (*j*) S. Kotha, A. Chandra Deb and R. Vinod Kumar, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1039–1043; (*k*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134–7186; (*l*) K. C. Nicolaou and J. S. Chen, *Chem. Soc. Rev.*, 2009, **38**, 2993–3009.

3 For review articles, see: (*a*) S. K. Chattopadhyay, S. Karmakar, T. Biswas, K. C. Majumdar, H. Rahman and B. Roy, *Tetrahedron*, 2007, **63**, 3919–3952; (*b*) A. Michaut and J. Rodriguez, *Angew. Chem., Int. Ed.*, 2006, **45**, 5740–5750; (*c*) A. Gradillas and J. Perez-Castells, *Angew. Chem., Int. Ed.*, 2006, **45**, 6086–6101; (*d*) A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199–2238; (*e*) M. D. McReynolds, J. M. Dougherty and P. R. Hanson, *Chem. Rev.*, 2004, **104**, 2239–2258; (*f*) A. Furstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3012–3043; (*g*) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18–29; (*h*) K. Sambasivarao, M. Milind and T. Arti, *Chem. Soc. Rev.*, 2009, **38**, 2065–2092.

4 For recent papers on organocatalytic TCRA reactions for C–C bond formation, see: (*a*) D. B. Ramachary, M. Kishor and K. Ramakumar, *Tetrahedron Lett.*, 2006, **47**, 651–656; (*b*) D. B. Ramachary, M. Kishor and G. Babul Reddy, *Org. Biomol. Chem.*, 2006, **4**, 1641–1646; (*c*) D. B. Ramachary and G. Babul Reddy, *Org. Biomol. Chem.*, 2006, **4**, 4463–4468; (*d*) D. B. Ramachary and M. Kishor, *J. Org. Chem.*, 2007, **72**, 5056–5068; (*e*) D. B. Ramachary, M. Kishor and Y. V. Reddy, *Eur. J. Org. Chem.*, 2008, 975–998; (*f*) D. B. Ramachary, Y. V. Reddy and B. V. Prakash, *Org. Biomol. Chem.*, 2008, **6**, 719–726; (*g*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2008, **6**, 4176–4187; (*h*) D. B. Ramachary, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.*, 2008, **6**, 4188–4197; (*i*) D. B. Ramachary, C. Venkaiah, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.*, 2009, **7**, 2053–2062; For recent papers on organocatalytic cascade and multi-component reactions, see: (*j*) D. B. Ramachary, K. Ramakumar and V. V. Narayana, *J. Org. Chem.*, 2007, **72**, 1458–1463; (*k*) D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2008, **6**, 2488–2492; (*l*) D. B. Ramachary, V. V. Narayana and K. Ramakumar, *Eur. J. Org. Chem.*, 2008, 3907–3911; (*m*) D. B. Ramachary, K. Ramakumar and V. V. Narayana, *Chem.–Eur. J.*, 2008, **14**, 9143–9147; (*n*) D. B. Ramachary and R. Sakthidevi, *Chem.–Eur. J.*, 2009, **15**, 4516–4522; (*o*) D. B. Ramachary, V. V. Narayana, M. S. Prasad and K. Ramakumar, *Org. Biomol. Chem.*, 2009, **7**, 3372–3378; (*p*) T. Bui and C. F. Barbas III, *Tetrahedron Lett.*, 2000, **41**, 6951–6954; (*q*) S.-I. Watanabe, A. Cordova, F. Tanaka and C. F. Barbas III, *Org. Lett.*, 2002, **4**, 4519–4522; (*r*) N. S. Chowdari, D. B. Ramachary and C. F. Barbas III, *Org. Lett.*, 2003, **5**, 1685–1688; (*s*) D. B. Ramachary, N. S. Chowdari and C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2003, **42**, 4233–4237; (*t*) D. B. Ramachary, K. Anebouselvy, N. S. Chowdari and C. F. Barbas III, *J. Org. Chem.*, 2004, **69**, 5838–5849; (*u*) D. B. Ramachary and C. F. Barbas III, *Chem.–Eur. J.*, 2004, **10**, 5323–5331; (*v*) D. B. Ramachary and C. F. Barbas III, *Org. Lett.*, 2005, **7**, 1577–1580; (*w*) J. W. Yang, M. T. Hechavarria Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036–15037; (*x*) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051–15053; (*y*) M. Marigo, T. Schulte, J. Franzen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 15710–15711; (*z*) S. Brandau, E. Maerten and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2006, **128**, 14986–14991; (*aa*) D. Enders, M. R. M. Huettl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861–863; (*bb*) D. Enders, M. R. M. Huettl, J. Runsink, G. Raabe and B. Wendt, *Angew. Chem., Int. Ed.*, 2007, **46**, 467–469; (*cc*) G.-L. Zhao, W.-W. Liao and A. Cordova, *Tetrahedron Lett.*, 2006, **47**, 4929–4932; (*dd*) R. Rios, H. Sunden, I. Ibrahem, G.-L. Zhao, L. Eriksson and A. Cordova, *Tetrahedron Lett.*, 2006, **47**, 8547–8551; (*ee*) W. Wang, H. Li, J. Wang and L. Zu, *J. Am. Chem. Soc.*, 2006, **128**, 10354–10355; (*ff*) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 3683–3686; (*gg*) H. Ishikawa, T. Suzuki and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2009, **48**, 1304–1307; (*hh*) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang and G. Zhong, *Org. Lett.*, 2008, **10**, 4585–4588.