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Parallel synthesis of individual shikimic acid-like molecules using a mixture-operation strategy and ring-closing enyne metathesis

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Abstract—Three new diastereomeric shikimic acid analogues (4-amino-3,5-dihydroxyl-cyclohex-1-en-carboxylic acids, **16**) bearing a C-4 amino group were synthesized in parallel by a mixture-operation protocol. Ring-closing enyne metathesis (RCEYM) under ethylene atmosphere was successfully employed to construct the desired carbocycles in high efficiency. The absolute configurations of each final product were confirmed by the 1D and 2D NMR techniques.

Olefin metathesis has attracted worldwide attention in organic synthesis as a versatile carbon–carbon bond formation method in recent years.[1] Metal carbene complex-catalyzed olefin metathesis has been known in polymer chemistry for about 40 years.[2] However, this reaction became practically useful in organic synthesis only when new catalysts were developed by Schrock and Grubbs since early 1990s (Fig. 1). Based on the types of olefins involved in the metathesis process, three categories that can be identified are diene,[1] enyne,[3] and diyne metathesis.[4] A variety of synthetically useful transformations have been developed on the basis of original olefin metathesis concepts, including ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMET), ring-opening metathesis (ROM), and cross-metathesis (CM or XMET). Among these, the RCEYM reaction is a uniquely powerful and atom economical method for the formation of dumbbell-shaped, multiply fused,[5] and bridged[6] ring systems possessing a 1,3-diene moiety via a tandem ring closure, if both the olefin and acetylene functionalities are suitably positioned in the linear substrates (Fig. 1). Herein, we report our recent results on the synthesis of amino acid-derived linear enyne precursors and subsequent generation of the carbocycles by ring closing enyne metathesis in high efficiency.[7]

The linear substrates bearing both olefin and acetylene functionalities for RCEYM reaction were prepared at first. Considering the stereochemical similarity to the influenza drug, Tamiflu, a stereogenic amino group was introduced into the substrates at C-4 position of the carbocycle in order to explore the further applications of those formed carbocycles in the future. The synthesis started from an optically active N-protected α-amino aldehyde **5** (easily prepared from cheaper L-serine (**1**)), which served as an equivalent of D-serinal (Scheme 1). After a simple two-step protection–deprotection manipulation, L-serinol **2** was converted to alcohol **4**. Swern oxidation of alcohol **4** afforded the corresponding aldehyde **5**, which was immediately treated with vinylmagnesium bromide (1.5 equiv) in THF at −78 °C and then to room temperature, giving a mixture of olefins **6a** and **6b** (ratio of **6a**:**6b** = 1.28:1, 96% yield in two steps). These two isomers could not be separated by the silica gel column chromatography and their ratio was determined by ^{1}H NMR. Determination of stereochemistry will be discussed in details together with three final targets **16** at the last stage.

To speed up the progress of parallel synthesis of substrates with similar functionalities, a mixture-based strategy was adopted in the following transformations

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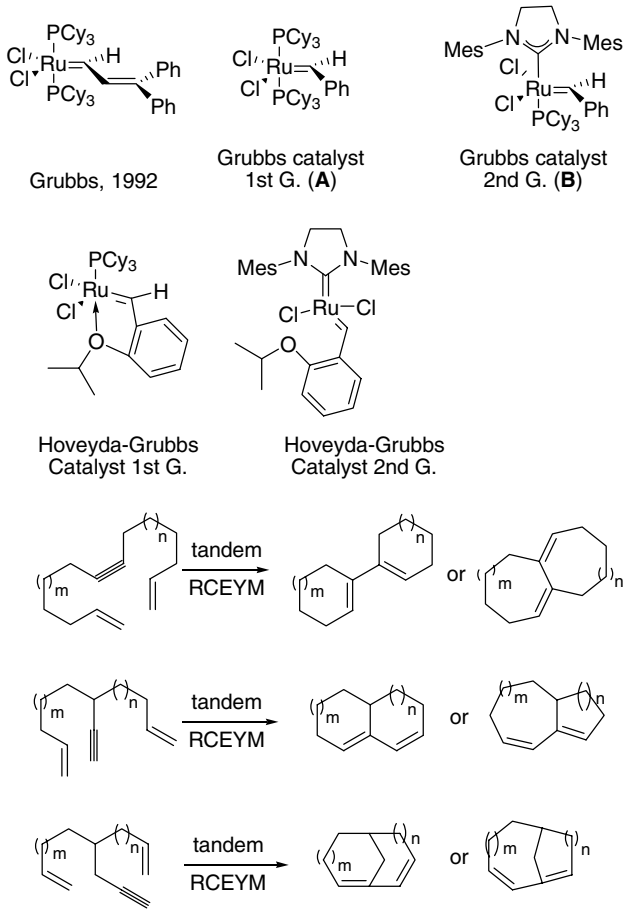
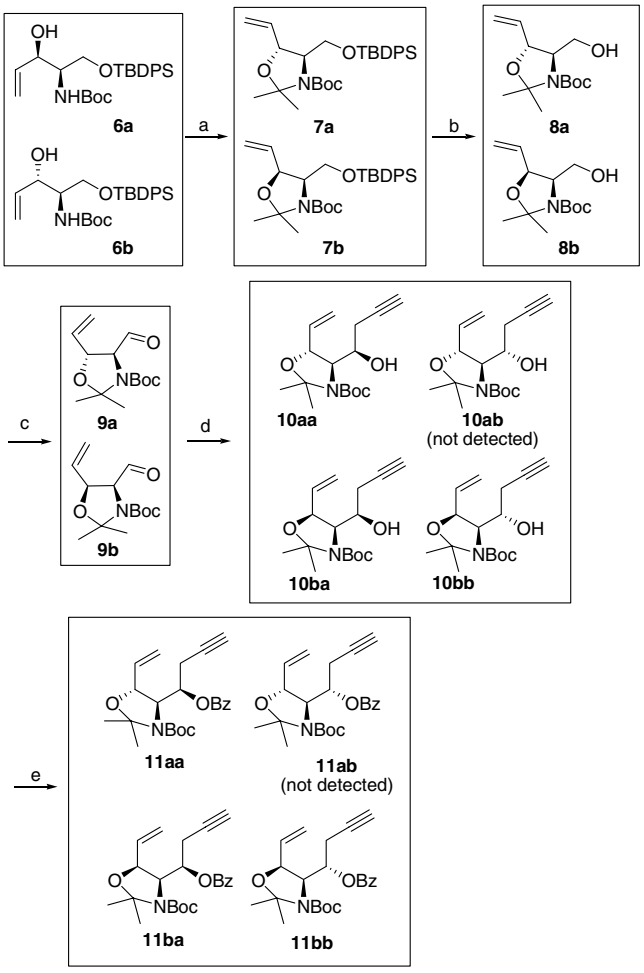
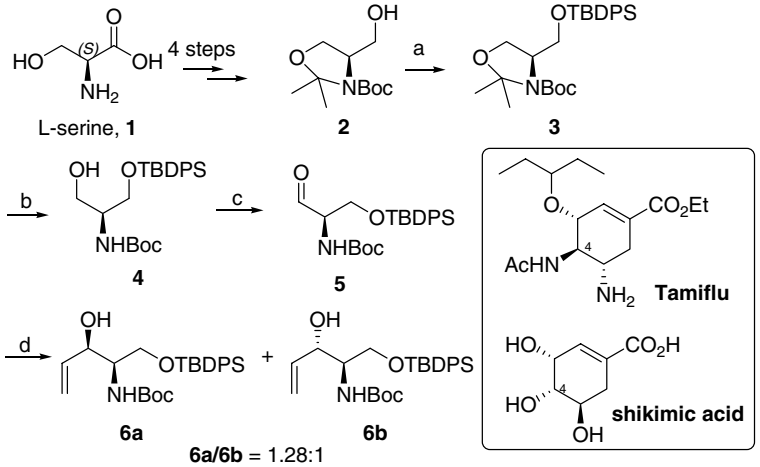


Figure 1. Representative catalysts for the olefin metathesis, and several typical ring systems formed by tandem RCEYMs.



Scheme 2. Reagents and conditions: (a) DMOP, PTSA (cat), DMF, 90 °C, 92%; (b) TBAF, THF, 70%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 100%; (d) conditions shown in Table 1; (e) BzCl, DMAP, Et_3N.

(Scheme 2). Treatment of the mixture of **6a** and **6b** with excess of 2,2-dimethoxypropane (DMOP) in DMF at 90 °C in the presence of catalytic amount of *p*-toluenesulfonic acid (PTSA) gave cyclic *N*,*O*-aminals **7** (92%). Subsequent desilylation of **7** by tetrabutylammonium fluoride (TBAF, 1.0 equiv) afforded alcohols **8**. Swern oxidation of alcohols **8** gave the corresponding aldehydes **9** (64% overall yield from alcohols **6**) as a mixture of two epimers, which was immediately treated with propargyl bromide (3.0 equiv) and activated zinc dust

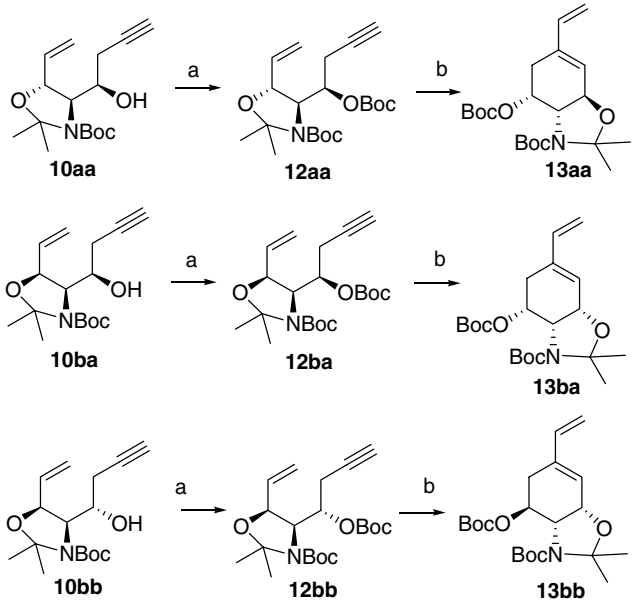


Scheme 1. Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, rt, 99%; (b) $BiBr_3$, acetonitrile, rt, 92%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C; (d) vinylMgBr, THF, −78 °C to 0 °C, 96% for two steps.

(4.0 equiv) in DMF–ether (1:1) to give a mixture of diastereomeric enynes **10** in 85% yield. Theoretically, all four possible stereoisomers of **10** could be generated by such a treatment. In deed, only three epimers (**10aa**, **10ba**, and **10bb**) were obtained from the mixture after careful isolation at this stage. The relative configurations of **10aa**, **10ba** and **10bb** were finally determined after further transformations in parallel to the acids **16**.

In order to make sure the crude products ratio (for more sensitive HPLC measurements by a UV-detection mode), a benzoic acid was then introduced to the crude mixture alcohols **10** through a standard ester bond formation reaction, giving a mixture of esters **11** (Scheme 2). The results are shown in Table 1. Obviously, zinc-promoted propargylation of **9a** gave **10aa** (*erythro*) as the only product. For **9b**, both **10ba** (*erythro*) and **10bb** (*threo*) were generated in similar ratio (**11ba**:**11bb** = 1.3:1 by HPLC). In order to obtain the fourth isomer **10ab** (*threo*), a number of propargylation conditions were attempted, including Zn–C_3H_3Br in DMF–ether, C_3H_3MgBr in THF and C_3H_3MgBr in THF–HMPA (Table 1). To our disappointment, all these efforts failed. Such results can be explained by our previously proposed model[8] that propargylation of carbonyl compounds with propargyl bromide and zinc dust favorably affords the *erythro*-diastereomer through a Felkin–Ahn transition state, and the *erythro*/*threo* selectivity is usually much higher if there is an oxygenated five-membered ring flanking the aldehyde group in the substrate. This means high steric congestion in the transition state favors *erythro* selectivity in the propargylation of aldehyde **9a**. As mentioned above, none **10ab** was detected though a variety of propargylation conditions were examined, even by changing the electronic factors of the nucleophile (see the above text). Obviously, steric factor of aldehyde **9a** is a key determinant in all examined propargylation reactions. Therefore, we stopped further endeavor to acquire **10ab**, and continued exploring our mixture-operation protocol.

With the above single epimers **10aa**, **10ba**, and **10bb** in hand, RCEYM reactions under ethylene atmosphere were examined. Our practice found that existence of the free hydroxyl group in substrates **10** affected the efficiency of cyclization severely. Therefore, all three linear enynes **10** were converted to the corresponding *O*-Boc protected compounds **12** by treatment with Boc_2O in acetonitrile at room temperature in the presence of catalytic amount of DMAP (Scheme 3). Further examination of the RCEYM reaction conditions under ethylene atmosphere showed that the 2nd generation Grubbs catalyst was generally more efficient with comparison of



Scheme 3. Reagents and conditions: (a) Boc_2O, DMAP, acetonitrile, 89% for **12aa**, 83% for **12ba**, and 85% for **12bb**; (b) 5 mol % of 2nd G catalyst (**B** in Fig. 1), CH_2Cl_2, ethylene atmosphere, rt, 91% for **13aa**, 97% for **13ba**, and 92% for **13bb**.

the 1st generation Grubbs catalyst. After optimizations, standard reaction conditions for enyne ring-closing metathesis were fixed to use 5 mol % of catalyst B and an initial 30–40 mM of substrate in CH_2Cl_2 under ethylene atmosphere (using an ethylene balloon). All three linear substrates **12** were smoothly converted to the corresponding 1-vinylcyclohexenes **13** in excellent yields. In a larger scale practice, it was found that these three carbocycles **13** were much easier to separate on the silica gel column chromatography. Therefore, our mixture-operation was continued until the completion of enyne metathesis.

As mentioned above, 1,3-dienes **13** are structurally very close to the skeleton of shikimic acid. Therefore, they could be the suitable precursors for the synthesis of shikimic acid-like molecules. (−)-Shikimic acid is a natural product with anti-thrombus and antitumor activities. Also, it is the major industrial starting material for the famous anti-influenza drug Tamiflu. Known as the shikimate pathway, (−)-shikimic acid occupies an important position in the biosynthesis pathway, along which three aromatic amino acids (L-phenylalanine, L-tyrosine, and L-tryptophan) are synthesized. More recently, shikimic acid was also used as a combinational template to synthesize natural product-like libraries with potential

Table 1. Results of propargylation of **9** under various conditions

Entry	Conditions[a]	Yield[a]	**10aa**:**10bb**:**10ba**[b]	**11aa**:**11bb**:**11ba**[c] (overall yield)
1	Zn, C_3H_3Br	83%	3.5:1:1.7	4.9:1:1.3 (89%)
2	C_3H_3MgBr	62%	1.6:1:1.9	2:1:1.4 (91%)
3	C_3H_3MgBr/HMPA	45%	3.3:1:1.8	7:1:1.7 (85%)

[a] For the propargylation step. All the reactions were performed in THF.
[b] Determined by ^{1}HNMR after column chromatography isolation.
[c] Determined directly by HPLC.

uses in drug development.[9] Today, shikimic acid receives much more attention including the synthesis of diverse analogues as a platform to find more selective and effective neuraminidase inhibitors. Using our synthesized six-membered carbocycles **13** as precursors, three shikimic acid analogues bearing a C-4 amino group (to replace its original hydroxyl group) were successfully synthesized. In parallel, regioselective oxidative cleavage of the terminal olefins in **13** by OsO_4–$NaIO_4$[10] followed by oxidation with $NaClO_2$ in ^{t}BuOH–water (4:1) gave the corresponding acids **15**. Global deprotection of **15aa/15ba/15bb** was finally carried out in a dichloromethane solution containing 10% TFA, affording the expected shikimic acid-like analogues **16aa/16ba/16bb** in quantitative yields,[11] respectively (Scheme 4).

Absolute configurations of the three final acids **16ba**, **16aa**, and **16bb** were determined by NMR experiments (^{1}H NMR, NOESY). Strong NOE between H-3, H-4, and H-5 of **16ba** was observed. Thus, H-3, H-4, and H-5 of **16ba** have cis–cis configuration. In **16aa**, strong NOE between H-4 and H-5 and comparatively weak NOE between H-3 and H-4 was observed. Combined with coupling constants showed by ^{1}H NMR ($J_{H\text{-}3,H\text{-}4} = 9.9$ Hz and $J_{H\text{-}4,H\text{-}5} = 2.2$ Hz), the relative configurations were easily determined as trans for H-3 and H-4, and cis for H-4 and H-5. In **16bb**, strong NOE between H-3 and H-4 was observed, and no NOE between H-4 and H-5 was found. Combined with coupling constants ($J_{H\text{-}3,H\text{-}4} = 4.5$ Hz and $J_{H\text{-}4,H\text{-}5} = 10.8$ Hz), the relative configurations were then determined as cis for H-3 and H-4, and trans for H-4 and H-5. With all these information, re-analysis of the NOESY and ^{1}H NMR of epimers of **16** again confirmed the above conclusion. The final absolute configurations of **16** are shown in Figure 2. Concomitantly, the absolute configurations of precursors **10** and **6** are also determined.

In conclusion, three new shikimic acid analogues **16** bearing an amino group at the C-4 position were synthesized in parallel through multiple steps of mixture operations. Sequential vinylmagnesium bromide addition and zinc-mediated propargylation of aldehydes, ring-closing enyne metathesis and regioselective oxidation of terminal olefin were successfuly performed in the syn-

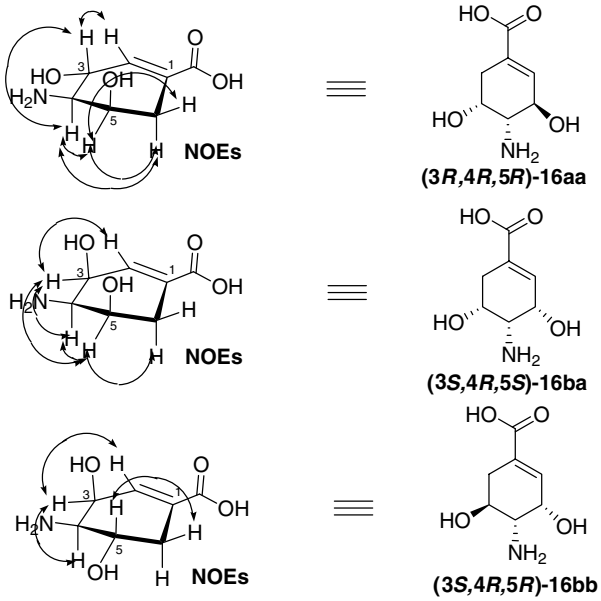
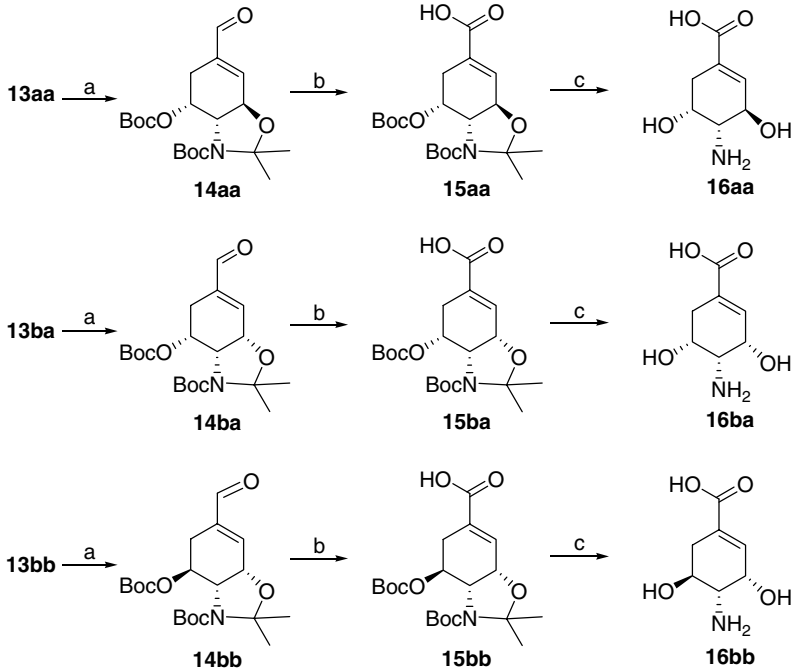


Figure 2. Illustration of NOESY result for final targets **16**.



Scheme 4. Reagents and conditions: (a) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane–water (3:1), 60%; (b) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, ^{t}BuOH–water (4:1), 100%; (c) TFA, DCM, 100%.

thesis. Commercially available L-serine was used as the starting material to introduce the first essential stereogenic center economically. Our illustrated protocol using a highly efficient RCEYM-based carbocycle-formation combined with mixture operations provides a fast track to those diverse molecules with similar structure to shikimic acid and Tamiflu, which have potential applications in today's new drug discovery including the neuraminidase inhibitors.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.118.

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11. Data for **16aa**: $[\alpha]_D^{25}$ −4.9 (*c* 0.45, MeOH/H_2O = 1:1); IR (KBr): 3195, 1668, 1552, 1438, 1399, 1204, 1138 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 6.59 (s, 1H), 4.61–4.58 (m, 1H), 4.45 (m, 1H), 3.38 (dd, J = 9.1, 2.2 Hz, 1H), 2.73–2.72 (m, 1H), 2.59 (d, J = 19.2Hz, 1H) ppm;^{13}C NMR (75 MHz, D_2O): δ 171.4, 136.6, 134.1, 68.4, 67.9, 58.9, 35.3 ppm; ESIMS (*m*/*z*, %): 174.1 ($M+H^+$, 100%); HRMS (ESI) Calcd for $C_7H_{12}NO_4$ ($M+H^+$): 174.0761. Found: 174.0768. Data for **16ba**: $[\alpha]_D^{23}$ 8.5 (*c* 0.18, MeOH/H_2O = 1:1). IR (KBr): 3379, 3181, 2891, 1544, 1401, 1368, 1347, 1326, 1309, 1078, 1060, 1037 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 6.44 (m, 1H), 4.49 (t, J = 4.5 Hz, 1H), 3.97 (ddd, J = 10.8, 9.3, 5.6 Hz, 1H), 3.25 (dd, J = 10.8, 4.2 Hz, 1H), 2.83 (dd, J = 17.4, 5.6 Hz, 1H), 2.21 (dd, J = 17.4, 9.3 Hz, 1H) ppm;^{13}C NMR (75 MHz, D_2O): δ 174.7, 136.8, 128.8, 64.0, 63.8, 55.5, 33.8 ppm; ESIMS (*m*/*z*, %): 174.1 ($M+H^+$, 100%). Data for **16bb**: $[\alpha]_D^{26}$ 11.6 (*c* 0.10, MeOH/H_2O = 1:1); IR (KBr): 3433, 3166, 1660, 1635, 1561, 1403, 1358, 1308, 1242, 1102, 1069 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 6.27 (s, 1H), 4.78 (s, 1H), 4.12–4.07 (m, 1H), 3.43 (s, 1H), 2.53 (dd, J = 18.0, 10.5 Hz, 1H), 2.18 (dd, J = 18.0, 7.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, D_2O): δ 177.4, 137.2, 133.4, 67.8, 67.7, 56.2, 32.6 ppm; ESIMS (*m*/*z*, %): 174.2 ($M+H^+$, 100%).