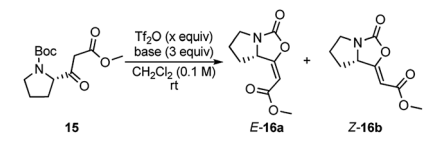




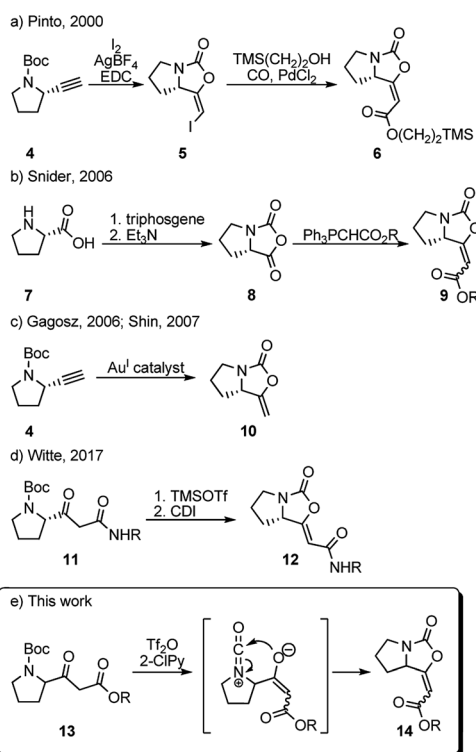
At the start of our investigation, model  $\beta$ -ketoester **15**, prepared from *N*-Boc-L-proline,<sup>7</sup> was chosen as the model substrate to identify optimal reaction conditions (Table 1). According to Kokotos' protocol,<sup>12c</sup> the initial using of 1.5 equivalents of  $\text{Tf}_2\text{O}$  and 3 equivalents of 2-ClPy led to a full conversion of the substrate **15** in 15 minutes (monitored by TLC) (Table 1, entry 7). The inspection of  $^1\text{H}$  NMR spectrum of the crude reaction mixture confirmed the presence of only desired product **16** almost exclusively as *E* isomer (*E/Z* ratio 93 : 7) which was isolated in 53% combined yield. Gratifyingly, lowering the amount  $\text{Tf}_2\text{O}$  (1.1 equiv.) resulted in a significant increase of the yield up to 80% with the slight decrease of *E* isomer **16a** (Table 1, entry 8).<sup>13</sup> Any variation of the amount of 2-ClPy did not have any positive impact on the reaction (Table 1, entries 9 and 10). The use of other 2-halopyridines reduced yield of **16** and prolonged reaction times were observed (Table 1, entries 11–13). For comparison, when we applied Witte's reaction conditions, yield dropped remarkably and *E/Z* selectivity disappeared completely (Table 1, entry 14). At last, we tested other bases commonly used in the combination with  $\text{Tf}_2\text{O}$ . Triethylamine, 4-dimethylaminopyridine, pyridine, and 2,6-lutidine resulted only in traces of product **16** (Table 1, entries 2–5), as well as when no base was used (Table 1, entry 1). Using DBU, enol-carbamate **16** was formed in slightly improved *E/Z* ratio (Table 1, entry 6). Nevertheless,  $^1\text{H}$  NMR spectrum of the crude reaction mixture showed the formation of a large amount of unidentified by-products and desired product was isolated only in 41% yield.

**Table 1** Optimization of the reaction conditions for cyclization of  $\beta$ -ketoester **15**



| Entry | $\text{Tf}_2\text{O}$         | Base                  | Time (min) | <b>16a</b> : <b>16b</b> <sup>a</sup> | Yield <sup>b</sup> (%) |
|-------|-------------------------------|-----------------------|------------|--------------------------------------|------------------------|
| 1     | 1.5                           | —                     | 60         | —                                    | — <sup>c</sup>         |
| 2     | 1.5                           | $\text{Et}_3\text{N}$ | 60         | —                                    | — <sup>c</sup>         |
| 3     | 1.5                           | DMAP                  | 60         | —                                    | — <sup>c</sup>         |
| 4     | 1.5                           | Pyridine              | 60         | —                                    | — <sup>c</sup>         |
| 5     | 1.5 <sup>d</sup>              | 2,6-Lutidine          | 60         | —                                    | — <sup>c</sup>         |
| 6     | 1.5 <sup>d</sup>              | DBU                   | 60         | 90 : 10                              | 41 <sup>e,f</sup>      |
| 7     | 1.5                           | 2-ClPy                | 15         | 93 : 7                               | 53 <sup>e</sup>        |
| 8     | 1.1                           | 2-ClPy                | 15         | 85 : 15                              | 80 <sup>e</sup>        |
| 9     | 1.1                           | 2-ClPy (1.5 equiv.)   | 40         | 85 : 15                              | 75 <sup>e</sup>        |
| 10    | 1.1                           | 2-ClPy (5 equiv.)     | 15         | 87 : 13                              | 64 <sup>e</sup>        |
| 11    | 1.1                           | 2-FPy                 | 15         | 89 : 11                              | 71 <sup>e</sup>        |
| 12    | 1.1                           | 2-BrPy                | 70         | 86 : 14                              | 73 <sup>e</sup>        |
| 13    | 1.1                           | 2-IPy                 | 90         | 86 : 14                              | 68 <sup>e</sup>        |
| 14    | Witte's protocol <sup>g</sup> |                       | Overnight  | 50 : 50                              | 36 <sup>e</sup>        |

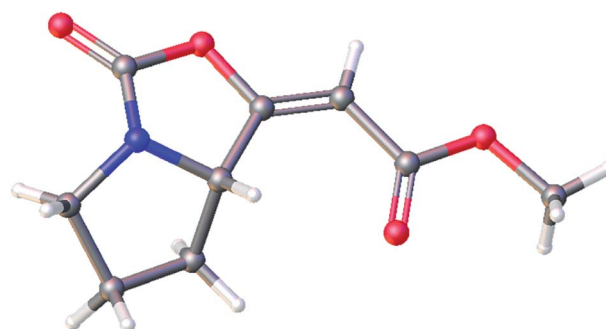
<sup>a</sup> Ratio determined by  $^1\text{H}$  NMR of the crude reaction mixture. <sup>b</sup> Isolated combined yield. <sup>c</sup> Traces of products. <sup>d</sup> Reactions performed with 1.1 equiv. of  $\text{Tf}_2\text{O}$  did not lead to full conversion of ester **15**. <sup>e</sup> Reactions were performed on 1 mmol of ester **15**. <sup>f</sup> Reaction mixture contained a large amount of unidentified by-products. <sup>g</sup> Reaction conditions: (1)  $\text{TMSOTf}$  (2 equiv.),  $\text{CH}_2\text{Cl}_2$ , 0 °C, 1 h. (2) CDI (1.5 equiv.),  $\text{CH}_2\text{Cl}_2$ , 0 °C – rt, overnight.<sup>7</sup>



**Scheme 1** Literature syntheses of bicyclic enol-carbamates and method proposed herein.

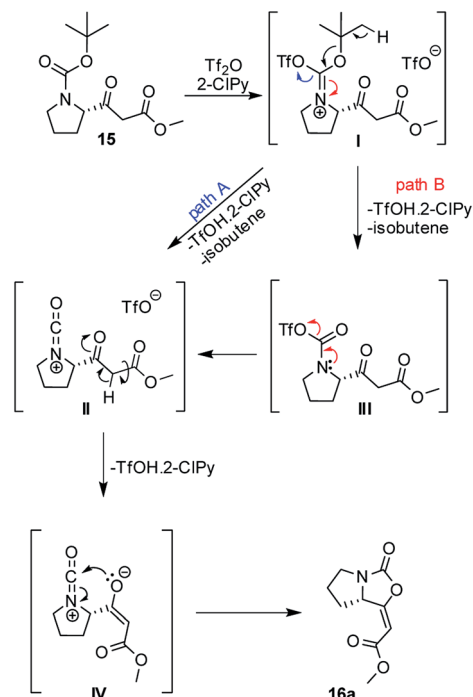
It is noteworthy that the reaction can be performed on a gram scale without affecting the yield and both isomers are easily separable by FCC (see the ESI<sup>†</sup>).

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of the major *E* isomer **16a** were consistent with those published previously.<sup>8</sup> Possible racemization in the course of the reaction was dismissed based on the comparing specific optical rotation with the published data for **16a** ( $[\alpha]_D^{22} = -261.1$  (*c* 1.01, MeOH); ref. 8:  $[\alpha]_D^{22} = -207$  (*c* 1.0, MeOH)). Most importantly, X-ray crystallographic analysis of **16a** (Fig. 2; see the ESI<sup>†</sup> for further details)<sup>14</sup> confirmed its absolute configuration on the C-7a carbon atom.



**Fig. 2** Molecular structure of the enol-carbamate *E*-**16a** confirmed by X-ray crystallographic analysis.

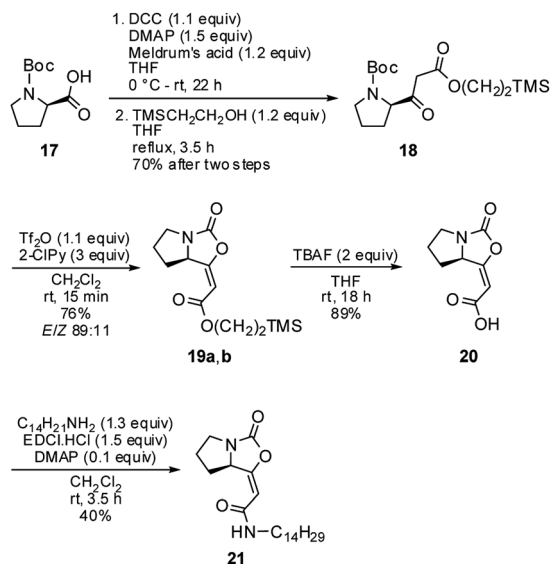




Scheme 2 Plausible mechanism of the cyclization  $\beta$ -ketoester **15**.

The minor *Z* isomer **16b** was isolated for the first time as the pure compound and was fully characterized. Its structure was assigned on the basis of its  $^1\text{H}$ ,  $^{13}\text{C}$ , COSY, HSQC, and HMBC NMR spectra.

A plausible mechanism of the cyclization of  $\beta$ -ketoester **15** was based upon previous works<sup>12a-c</sup> and it is depicted in Scheme 2. Isocyanate cation **II**, as a key intermediate, can be formed directly from iminium triflate **I** (path A) or through the formation of carbamoyl triflate **III** with subsequent elimination of triflate ion spontaneously (path B). Ester enolate moiety **IV** then reacts as *O*-



Scheme 3 Synthesis of the brabantamide A analogue **21**.

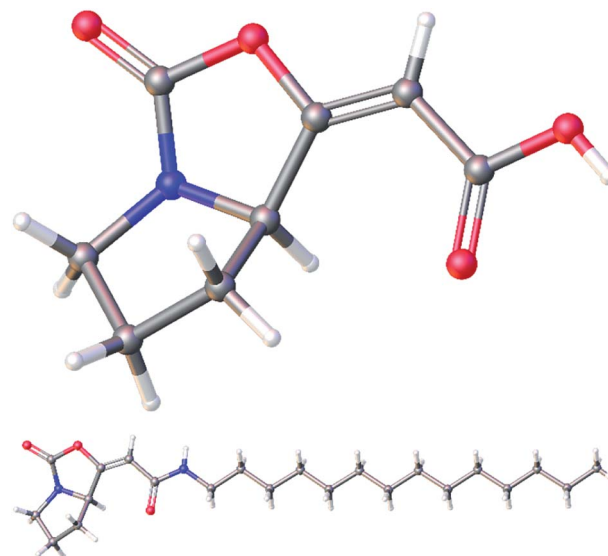


Fig. 3 Molecular structures of acid **20** (top) and amide **21** (bottom) confirmed by X-ray crystallographic analysis.

nucleophile *via* 5-*endo-dig* cyclization and leads predominantly to the formation of the enol-carbamate **16a**.

Next, the optimized conditions were briefly applied in the synthesis of the brabantamide A analogue **21** (Scheme 3). Starting  $\beta$ -ketoester **18** was synthesized in two steps in a 70% yield using both commercially available *N*-Boc-D-proline **17** and 2-(trimethylsilyl)ethanol. It ought to be mentioned that previously examined hydrolysis of the corresponding methyl ester **16a** under acidic as well as basic conditions failed due to the instability of the bicyclic enol-carbamate.<sup>3,8</sup>

Subsequent cyclization of ester **18** using optimized reaction conditions afforded enol-carbamate **19** in 76% yield as a mixture of *E* and *Z* isomers in a ratio of 89 : 11. After isolation of the major isomer *E*-**19a**, it was treated with TBAF, providing free acid **20** in 89% yield. Finally, an amidation of **20** with tetradecylamine in the presence of EDCI gave amide **21** in moderate 40% yield. Both free acid **20** and amide **21** were fully characterized for the first time and their structures were assigned on the basis of its  $^1\text{H}$ ,  $^{13}\text{C}$ , COSY, HSQC, and HMBC NMR spectra. Moreover, their structures were unambiguously confirmed by X-ray crystallographic analysis (Fig. 3; see ESI† for further details).<sup>14</sup>

## Conclusions

In conclusion, a new method of preparing bicyclic enol-carbamates with exocyclic double bond has been developed. Bicyclic oxazolidinone framework was obtained in one step from readily available  $\beta$ -ketoesters in very good yields and with high *E/Z* selectivity under mild reaction conditions using  $\text{Tf}_2\text{O}$  and 2-chloropyridine tandem. The simplicity of this method was exemplified by a short and effective synthesis of the analogue of brabantamide A from commercially available *N*-Boc-D-proline in five steps with an overall 17% yield.



## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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