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Tandem cross metathesis and intramolecular aza-Michael reaction to synthesize bicyclic piperidines and indolizidine 167E

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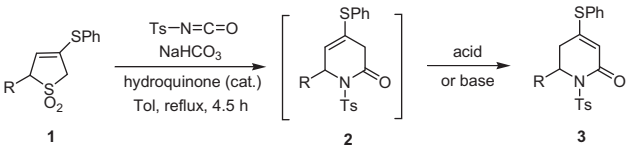
ABSTRACT

We have successfully transformed the terminal alkenes of dihydropyridones to the α,β-unsaturated esters by cross metathesis (CM). After detosylation the secondary amides can undergo the intramolecular aza-Michael reaction to give the bicyclic piperidine structures. The stereoselectivity of the aza-Michael reaction is determined by the size of the newly formed ring. With simple transformations we have also achieved the synthesis of indolizidine 167E.

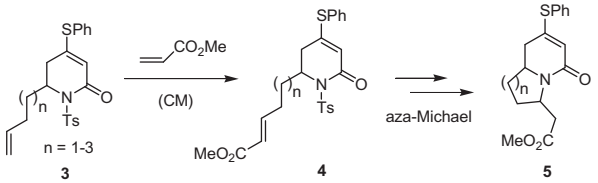
The piperidine ring is among the most abundant molecular fragments in both natural and synthetic compounds with various biological activities.[1] The aza-Diels–Alder reaction is one of the most versatile routes to substituted piperidines.[2] Among the piperidine natural products are the bicyclic indolizidines and quinolizidines.[3] We have reported a new aza-Diels–Alder reaction of thio-substituted 3-sulfolenes (**1**) with *p*-toluenesulfonyl isocyanate (PTSI) to give the cyclized products **2** which upon treatment with acid or base afford the conjugated products **3** (Scheme 1),[4] and we have used this method to synthesize some indolizidines and quinolizidines.[5]

Cross metathesis (CM) is a convenient route to make functionalized olefins from simple alkenes.[6] We now describe the combination of CM with our previous aza-Diels–Alder methodology to synthesize tetrahydropyridinones **4** containing the α,β-unsaturated ester group, which upon *N*-detosylation can undergo intramolecular aza-Michael reaction[7,8] to give the bicyclic piperidine products **5** (Scheme 2).

We first studied the CM reactions of compound **3b** with methyl acrylate (10 equiv) in toluene in the presence of the Grubbs' catalysts **G1** and **G2** to give the conjugated ester **4b** (Table 1). The use of **G1** under microwave heating at 150 °C did not give any CM product **4b** (entry 1). Inclusion of *p*-cresol (0.5 equiv) gave a very low yield of product **4b** (entry 2), probably because *p*-cresol could stabilize the Grubbs' catalyst.[9] Use of catalyst **G2** under microwave heating (entry 3) gave a good yield of **4b**. This might be due to higher thermal stability of **G2** as compared to **G1**. However, some unreacted starting material was still recovered. Addition of *p*-cresol (0.5 equiv) completed the reaction and further increased the yield of **4b** (entry 4). Thermal heating in refluxing toluene with catalyst **G2** and *p*-cresol also gave a good yield of **4b**, but required a much longer time (entry 5). Under the above standard reaction conditions (Table 1, entries 4 and 5), the CM products **4a** and **4c** were also obtained in good yields (Table 2). The CM reactions were also carried out under thermal conditions all gave slightly lower yields



Scheme 1. Preparation of dihydropyridones **3**.



Scheme 2. Tandem cross-metathesis and aza-Michael reaction.

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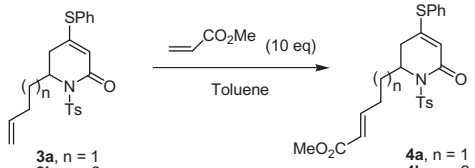
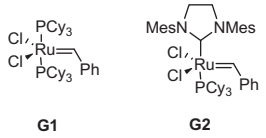
Table 1
Cross metathesis of compound **3b** with methyl acrylate



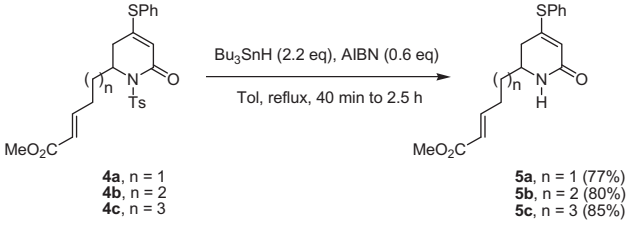


Entry	Cat.	Reaction conditions	Product (%Yield)
1	G1	MW, 150 °C, 30 min	NR
2	G1	*p*-cresol (0.5 equiv), MW, 150 °C, 3.5 h	**4b** (16), **3b** (60)
3	G2	MW, 150 °C, 30 min	**4b** (88), **3b** (10)
4	G2	*p*-cresol (0.5 equiv), MW, 150 °C, 30 min	**4b** (96)
5	G2	*p*-cresol (0.5 equiv), reflux, 3.5 h	**4b** (91)

Table 2
CM reactions of compounds **3** under microwave and thermal conditions

Entry	3	Product	%Yield (condition)
1	**3a**	**4a**	91 (A)[a]; 85 (B)[b]
2	**3b**	**4b**	96 (A); 91 (B)
3	**3c**	**4c**	94 (A); 88 (B)

[a] Condition A: *p*-cresol (0.5 equiv), toluene, MW, 150 °C, 30 min.
[b] Condition B: *p*-cresol (0.5 equiv), toluene, reflux, 3.5 h.



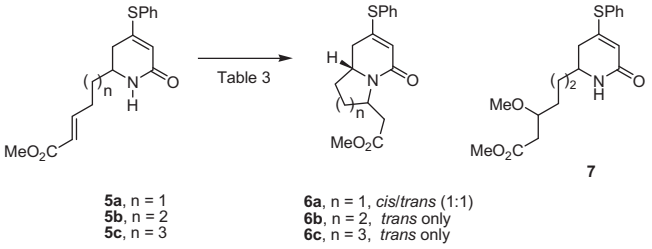
Scheme 3. Detosylation of compounds **4**.

and required a longer reaction time than those under microwave conditions. The α,β-unsaturated ester group of compounds **4** was assigned as the *trans* C=C double bond from the coupling constants of their ^{1}H NMR spectra.

The *N*-tosyl group of amides **4a–c** was cleaved without affecting the α,β-unsaturated ester group by the Parsons' method[10] of Bu_3SnH/AIBN. The lactams **5a–c** were obtained in good yields (Scheme 3).

The reaction of compounds **5a–c** with base was then studied, and the results are summarized in Table 3. Reaction of compound **5b** with a catalytic amount of NaOH in refluxing MeOH gave the desired aza-Michael product **6b** only in low yield, together with a significant amount of unreacted starting material **5b** and the methoxide addition product **7** (entry 1). Heating compound **5b** in a sealed tube at 100 °C (entry 2) led to an even lower yield of product **6b**. The reaction of compound **5b** with NaH (0.5 equiv) in refluxing THF, however, gave a good yield of product **6b** (entry 3) as a single diastereomer. Similar reaction of compound **5a** with NaH/THF (entry 4) also gave a good yield of product **6a**, but as a 1:1 mixture of *cis*/*trans* isomers as determined by ^{1}H NMR. Reaction at room temperature (entry 5) still gave the same result. The reaction of compound **5c** with NaH in refluxing THF (entry 6) gave only the recovered starting material. Formation of a seven-membered ring was probably disfavored by the entropy factor. Heating the reaction mixture in a sealed tube at 110 °C (entry 7), however, resulted in the formation of product **6c** as a single diastereomer in fair yield. The *trans* stereochemistry of compounds **6b** and **6c** was determined by their NOESY spectra, which showed cross signals between α-hydrogens of the ester group and hydrogen at the ring junction (Fig. 1).

Table 3
Intramolecular aza-Michael reaction of compounds **5b–d**



Entry	5	Reaction Conditions	Product (%Yield)[a]
1	**5b**	NaOH (0.1 equiv), MeOH, reflux, 4.5 h	**6b**:**7**:**5b** (29:29:42)[b]
2	**5b**	NaOH (0.1 equiv), MeOH, sealed tube, 100 °C, 4 h	**6b**:**7**:**5b** (10:31:59)[b]
3	**5b**	NaH (0.5 equiv), THF, reflux, 20 min	**6b** (88)
4	**5a**	NaH (0.5 equiv), THF, reflux, 20 min	**6a** (72)[c]
5	**5a**	NaH (0.5 equiv), THF, rt, 20 min	**6a** (74)
6	**5c**	NaH (0.5 equiv), THF, reflux, 7 h	NR
7	**5c**	NaH (0.5 equiv), THF, sealed tube, 110 °C, 30 min	**6c** (48)

[a] Isolated yield of the purified product.
[b] The ratio was determined from the crude ^{1}H NMR.
[c] The 1:1 ratio of *cis*/*trans* isomers was determined by ^{1}H NMR.

Based on the literature results of the diastereoselectivity of aza-Michael reactions[11] and the Curtin–Hammett principle,[12] we propose the mechanism for stereospecific formation of *trans* bicyclic products **6b** and **6c** as in Scheme 4. The antiperiplanar transition state involved in structure **A** has lower energy than the synclinal transition state involved in structure **B** not only because the former has better orbital overlap but also due to the A[1,3] strain present in the latter. However, the antiperiplanar approach **A** would not be as favorable when the tether is one carbon short for compound **5a** ($n = 0$ in Scheme 4). Hence product **6a** was obtained as a 1:1 mixture of *cis* and *trans* isomers.

Further treatment of the 1:1 *cis*/*trans* mixture of compound **6a** with $LiAlH_4$ at low temperature gave products **8a** and **8b**, which could be separated by column chromatography (Scheme 5). The stereochemistry of compounds **8a** and **8b** was confirmed by the NOESY spectra, and the structure of compound **8a** was also established by X-ray crystallography (Fig. 2).

Bromination of compound **8a** with PBr_3, followed by treatment with Bu_3SnH/AIBN led to the debromination product **9** (Scheme 6). Further reaction with Raney nickel both cleaved the C–S bond and

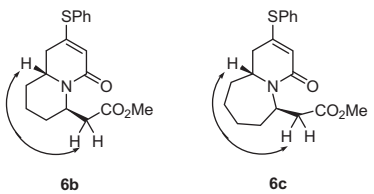
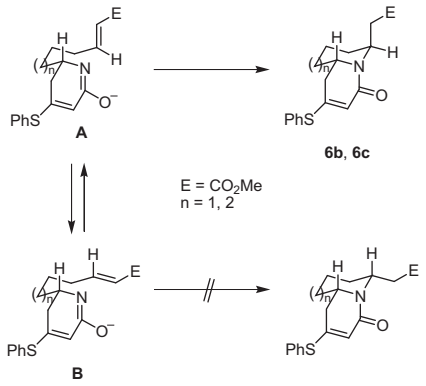
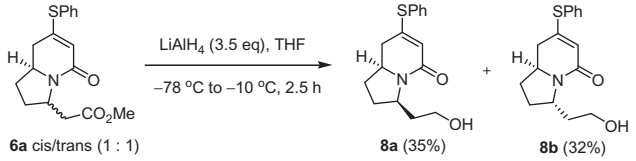


Figure 1. NOESY correlations of compounds **6b** and **6c**.



Scheme 4. Stereospecific formation of *trans*-**6b** and **6c**.



Scheme 5. Reduction of *cis*- and *trans*-**6a**.

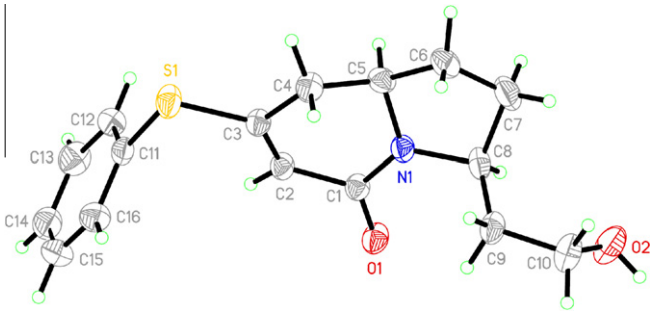
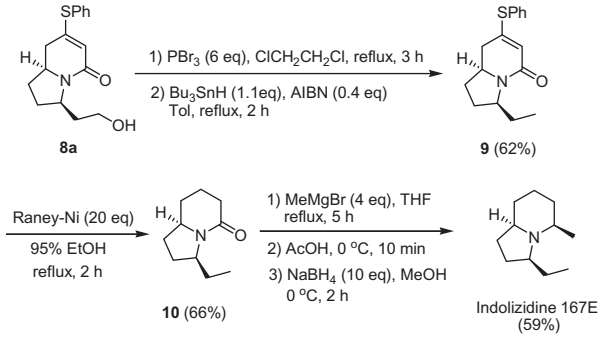


Figure 2. X-ray crystal structure of compound **8a**.



Scheme 6. Synthesis of indolizidine 167E.

reduced the C=C bond to give product **10**. Following a reported procedure,[13] the treatment of compound **10** with methylmagnesium bromide, followed by acidification with acetic acid, and reduction with sodium borohydride, gave indolizidine 167E, which was isolated from the venom of the ant *Solenopsis* (*Diplorhoptrum*) *conjurata*.[14] Only two syntheses of indolizidine 167E have been reported.[15]

In summary, we have successfully transformed the terminal alkenes **3a–c** to the α,β-unsaturated esters **4a–c** by cross metathesis (CM). After detosylation the amides **5a–c** can undergo the intramolecular aza-Michael reaction to give sulfur-substituted bicyclic compounds **6a–c**, the stereoselectivity of which is determined by the size of the newly formed ring. With simple transformations we have also achieved the synthesis of indolizidine 167E from compound **6a**.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.031.

References and notes

1. Rubiralta, M.; Giralt, E.; Diez, E. *Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991.
2. (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: Orlando, FL, 1987; (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813; (c) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558–3588; (d) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138.
3. (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, NY, 1986; vol. 3,. Chapter 1 For a recent review, see: (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603–626.
4. (a) Chou, S. S. P.; Hung, C. C. *Tetrahedron Lett.* **2000**, *41*, 8323–8326; (b) Chou, S. S. P.; Hung, C. C. *Synthesis* **2001**, 2450–2462.
5. (a) Chou, S. S. P.; Chiu, H. C.; Hung, C. C. *Tetrahedron Lett.* **2003**, *44*, 4653–4655; (b) Chou, S. S. P.; Ho, C. W. *Tetrahedron Lett.* **2005**, *46*, 8551–8554; (c) Chou, S. S. P.; Liang, C. F.; Lee, T. M.; Liu, C. F. *Tetrahedron* **2007**, *63*, 8267–8273; (d) Chou, S. S. P.; Liu, C. F. *J. Chin. Chem. Soc.* **2010**, *57*, 811–819; (e) Chou, S. S. P.; Cai, Y. L. *Tetrahedron* **2011**, *67*, 1183–1186; (f) Chou, S. S. P.; Yang, T. H.; Wu, W. S.; Chiu, T. H. *Synthesis* **2011**, 759–763; (g) Chou, S. S. P.; Wu, C. J. J. *Tetrahedron* **2012**, *68*, 1185–1191; (h) Chou, S. S. P.; Lu, C. L.; Hsu, Y. H. *J. Chin. Chem. Soc.* **2012**, *59*, 365–372; (i) Chou, S. S. P.; Wu, C. J. J. *Tetrahedron* **2012**, *68*, 5025–5030.
6. (a) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417–10418; (b) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277–1279; (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370; (d) Lesma, G.; Colombo, A.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 590–596; (e) Fustero, S.; Jimenez, D.; Rosello, M. S.; Pozo, C. D. *J. Am. Chem. Soc.* **2007**, *129*, 6700–6701; (f) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125–1132.
7. For some recent reviews, see: (a) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633–639; (b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058–11076; (c) Reyes, E.; Fernandez, M.; Uria, U.; Vicario, J. L.; Badia, D.; Carrillo, L. *Curr. Org. Chem.* **2012**, *16*, 521–546.
8. For some recent examples, see: (a) Ghorai, M. K.; Halder, S.; Das, R. K. *J. Org. Chem.* **2010**, *75*, 7061–7072; (b) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8666–8669; (c) Fustero, S.; Monteagudo, S.; Sanchez-Rosello, M.; Flores, S.; Barrio, P.; del Pozo, C. *Chem. Eur. J.* **2010**, *16*, 9835–9845; (d) Fustero, S.; del Pozo, C.; Mulet, C.; Lazaro, R.; Sanchez-Rosello, M. *Chem. Eur. J.* **2011**, *17*, 14267–14272; (e) Zhong, C.; Wang, Y.; Hung, A. W.; Schreiber, S. L.; Young, D. W. *Org. Lett.* **2011**, *13*, 5556–5559.
9. (a) Forman, G. S.; McConnell, A. E.; Tooze, R. P.; van Rensburg, W. J.; Meyer, W. H.; Kirk, M. M.; Dwyer, C. L.; Serfontein, D. *Organometallics* **2005**, *24*, 4528–4542; (b) Chou, C.-Y.; Hou, D.-R. *J. Org. Chem.* **2006**, *71*, 9887–9890; (c) Chen, L.-J.; Hou, D.-R. *Tetrahedron Asymmetry* **2008**, *19*, 715–720.
10. Parsons, A. F.; Pettifer, R. M. *Tetrahedron Lett.* **1996**, *37*, 1667–1670.
11. (a) McAlonan, H.; Stevenson, P. J.; Thompson, N.; Treacy, A. B. *Synlett* **1997**, 1359–1360; (b) Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T.; Nemoto, H. *Tetrahedron* **1999**, *55*, 15209–15229; (c) Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 275–278; (d) McAlonan, H.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 5411–5414; (e) Yu, S.; Pu, X.; Cheng, T.; Wang, R.; Ma, D. *Org. Lett.* **2006**, *8*, 3179–3182.
12. (a) Eliel, E. L. *Stereochemistry of Carbon Compounds*; New York: Mc-Graw-Hill, 1962. pp. 151-152, 237-238; (b) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.
13. (a) Yuguchi, M.; Tokuda, M.; Orito, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1031–1032; (b) Bates, R. W.; Song, P. *Synthesis* **2009**, 655–659.
14. Jones, T. H.; Hight, R. J.; Blum, M. S.; Fales, H. M. *J. Chem. Ecol.* **1984**, *10*, 1233–1249.
15. (a) Takahata, H.; Bandoh, H.; Momose, T. *Tetrahedron* **1993**, *49*, 11205–11212; (b) Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879–8882.