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Efficient Synthesis of Fused Bicyclic Glutarimides. Its Application to (±)-Alloyohimbane and Louisianin D

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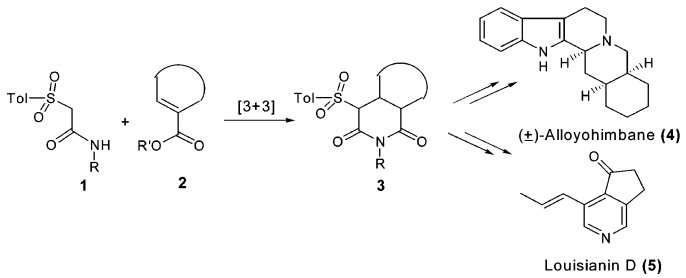
ABSTRACT



The reaction of α-sulfonyl acetamide 1 with various cyclic unsaturated esters 2 to fused bicyclic glutarimides is reported. Syntheses of (±)-alloyohimbane (4) and louisianin D (5) have been accomplished.

Bicyclic pyridines, piperidines, δ-lactams, and 2-pyridones are important core structures that are found in numerous biologically active compounds.[1] Although many methods have been reported for the synthesis of such compounds,[2] we envisioned that our previously developed [3+3] annulation of α-sulfonyl acetamide with α,β-unsaturated esters to give polysubstituted glutarimides[3] would be ideal for constructing fused bicyclic glutarimides which could be further converted to nitrogen-containing polycyclic alkaloids.[2b,4]

Thus, the reaction of α-sulfonyl acetamide **1** with various cyclic unsaturated esters **2** was investigated. The results are shown in Table 1. It is interesting to note that **3a** and **3b** are both cis-fused bicyclic compounds. The structures of **3a** and **3b** were unequivocally established by single-crystal X-ray

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(1) (a) Frederlesen, S. M.; Stermitz, F. R. *J. Nat. Prod.* **1996**, *59*, 41. (b) Stefanska, A. L.; Cassel, R.; Ready, S. J.; Warr, S. R. *J. Antibiot*. **2000**, *53*, 357. (c) Nakamura, M.; Kido, K.; Kinjo, J.; Nohara, T. *Phytochemistry* **2000**, *53*, 253. (d) Nakamura, M.; Chi, Y.-M.; Yan, W.-M.; Yonezawa, A.; Nakagugi, Y.; Toyokichi, Y.; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S. *Planta Med*. **2001**, *67*, 114. (e) Skaltsounis, A.-L.; Michel, S.; Tillequin, F.; Koch, M.; Pusset, J.; Chauviere, G. *Helv. Chim. Acta* **1985**, *68*, 1679. (f) Cook, C. E.; Wani, M. C.; Jump, J. M.; Jee, Y. M.; Fail, P. A. *J. Med. Chem*. **1995**, *38*, 753. (g) Ho, H. Y.; Chow, Y. S. *J. Chem. Ecol*. **1993**, *19*, 39. (h) Torsell, K.; Wahlberg, K. *Acta Chem. Scand*. **1967**, *21*, 53. (i) Scott, J. A.; Crews, F. T. *J. Pharmacol. Exp. Ther*. **1983**, *224*, 640.

(2) For pyridines, see: (a) Jones, K.; Escudero-Hernandez, M. L. *Tetahedron* **1998**, *54*, 2275. (b) John, K.; Fiumana, A.; Escudero-Hernandez, M. L. *Tetrahedron* **2000**, *56*, 397. For piperidines, see: (c) Hong, B.-C.; Gupta, A. K.; Wu, M.-F.; Liao, J.-H.; Lee, G.-H. *Org. Lett*. **2003**, *5*, 1689. (d) Gunter, M.; Gais, H.-J. *J. Org. Chem*. **2003**, *68*, 8037. For δ-lactams, see: (e) Li, T.-T.; Lesko, P.; Ellison, R. H.; Subramanian, N.; Fried, J. H. *J. Org. Chem*. **1981**, *46*, 111. (f) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aube, J. *Tetrahedron* **1997**, *48*, 16241. For 2-pyridones, see: (g) Yamamoto, Y.; Takagish, H.; Itoh, K. *Org. Lett*. **2001**, *3*, 2117.

(3) Chang, M.-Y.; Chang, B.-R.; Tai, H.-M.; Chang, N.-C. *Tetahedron Lett*. **2000**, *41*, 10273.

(4) (a) Bergmeier, S. C.; Seth, P. P. *J. Org. Chem*. **1999**, *64*, 3237. (b) Beierle, J. M.; Osimboni, E. B.; Metallinos, C.; Zhao, Y.; Kelly, T. R. *J. Org. Chem*. **2003**, *68*, 4970. (c) Kogure, N.; Nishiya, C.; Kitajima, M.; Takayama, H. *Tetahedron Lett*. **2005**, *46*, 5857.

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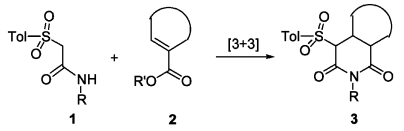
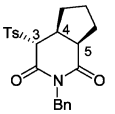
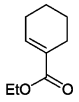
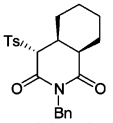
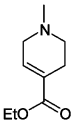
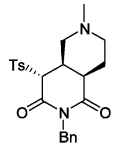
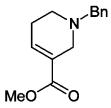
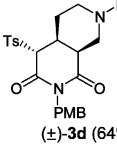
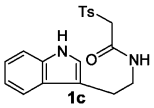
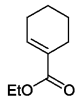
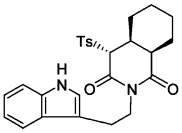
Table 1. Formation of Fused Bicyclic Glutarimides



Entry	α-sulfonyl amide	Michael acceptor	product (yleid %)
1	 **1a**	 **2a**	 (±)-**3a**(88%)[a]
2	 **1a**	 **2b**	 (±)-**3b** (83%)[a]
3	 **1a**	 **2c**	 (±)-**3c** (64%)[a]
4	 **1b**	 **2d**	 (±)-**3d** (64%)[a]
5	 **1c**	 **2e**	 (±)-**3e** (35%)[a]

[a] All yields were based on α-toluenesulfonyl acetamide.

analysis (Figure 1). The stereochemistries of **3c**−**e** were determined by comparing their ^{1}H NMR spectra with those of **3a** and **3b**.

To demonstrate the utility of this one-pot process, the formal synthesis of (±)-alloyohimbane (**4**) was investigated. As shown in Scheme 1, regioselective reduction of **3e** by sequential addition of triethylamine in THF and LAH reduction at refluxing temperature furnished **6**. Treatment of **6** with sodium amalgam gave 4,5-annulated lactam **7**. The spectral data of **7** were in agreement with those reported in the literature.[4a] Lactam **7** has been converted to alloyohimbane (**4**).[4a,5] Thus, the formal synthesis of alloyohimbane (**4**) was accomplished.

For the synthesis of louisianin D (**5**)[4b] produced by a species of *Streptomyces*,[6] glutarimide **3a** was chosen as the

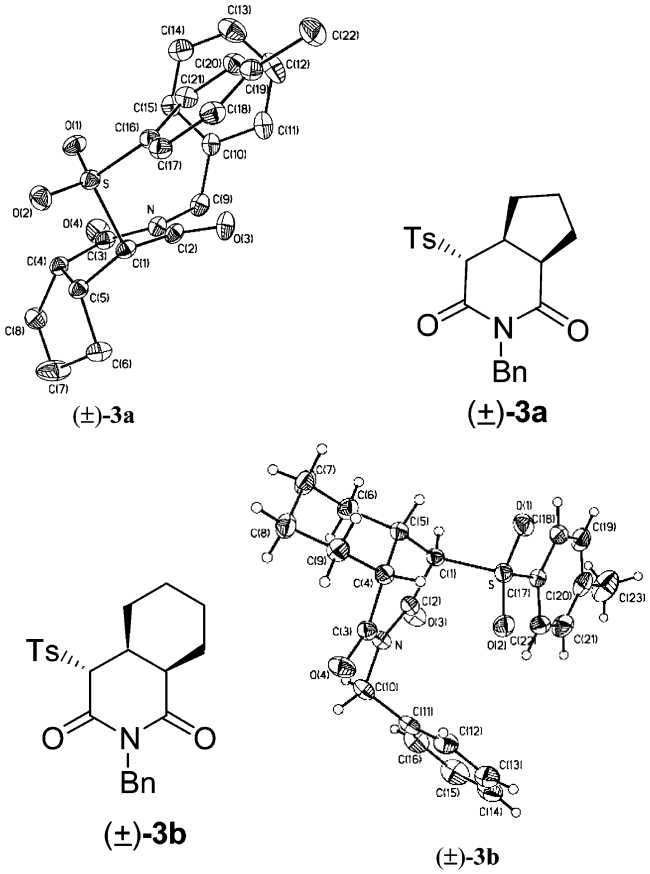
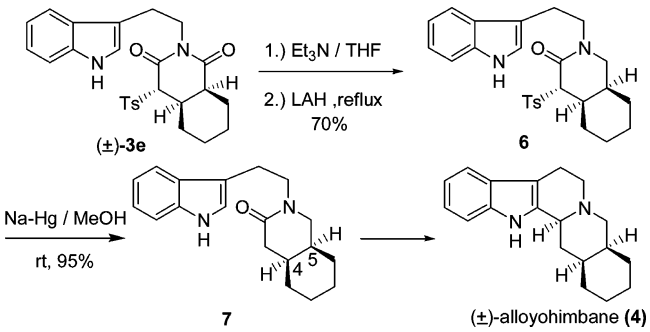


Figure 1. X-ray structures of (±)-**3a** and (±)-**3b**.

starting material. Following the procedure developed in our laboratory,[7] **3a** was reduced regioselectively to the corresponding hydroxylactam **8**. Treatment of **8** with boron triflouride furnished enlactam **9**. Allylation of **9** followed by dehydrosulfonation produced double-bond migrated 2-pyridone **10**. To accomplish the synthesis of louisianin D, **10** was first converted to the corresponding 2-chloropyridine **11**, which was then reduced to bicyclic pyridine **12** by treatment of **11** with zinc in acetic acid.[8] Regioselective hydroxylation of **12** with LHMDS and oxygen yielded **13**,[9] which was then further oxidized with the swern-oxidation

Scheme 1. Formal Synthesis of (±)-Alloyohimbane



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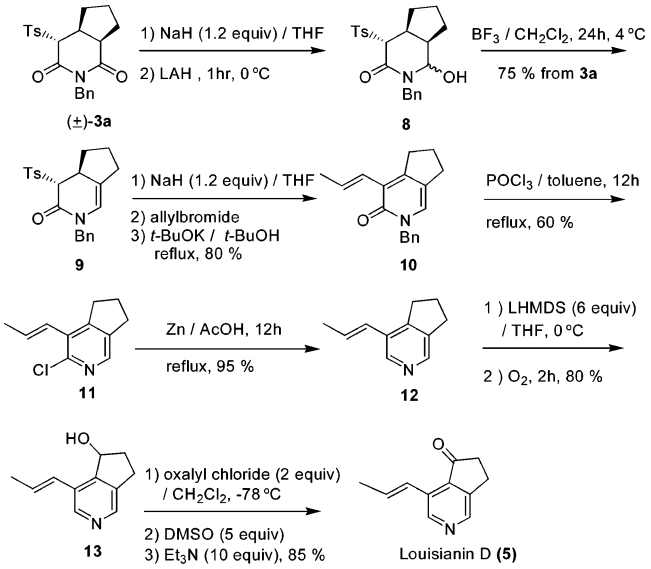
Scheme 2. Total Synthesis of Louisianin D



reagent to afford **5** (Scheme 2). The spectral data of **5** were in agreement with those reported in the literature.[6]

In conclusion, we have developed a one-pot reaction procedure to cis-fused bicyclic glutarimides. Syntheses of (±)-alloyohimbane (**4**) and louisianin D (**5**) were reported. Further application of fused bicyclic glutarimides to more complicated pentacyclic indole alkaloids is underway in our laboratory.

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Supporting Information Available: Additional spectroscopic data for all new compounds (^{1}H NMR in $CDCl_3$) and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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