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Synthesis of (+)-Elaeokanine A and (+)-Elaeokanine C Based upon a Novel Approach Involving Diastereoselective, Nucleophilic Addition to *N*-Acyliminium Ion and Retro Diels-Alder Reaction

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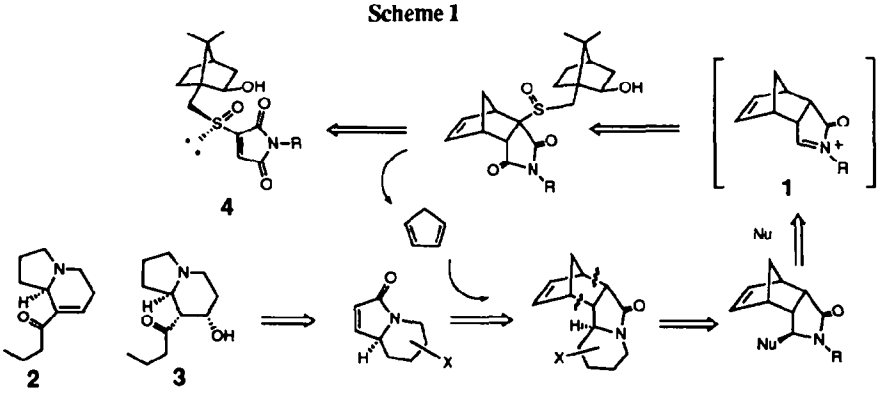
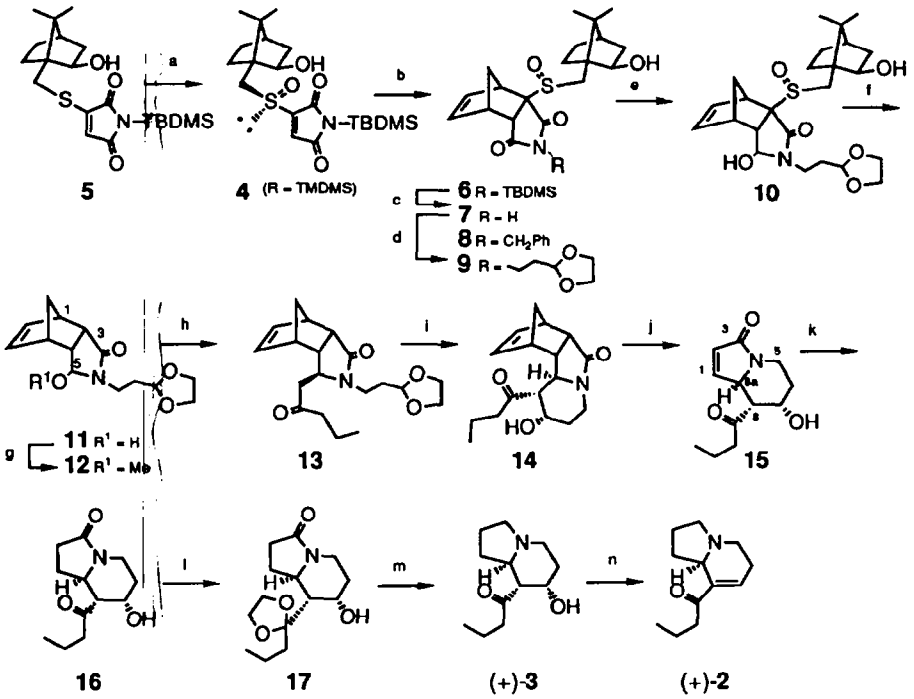
Abstract: An asymmetric synthesis of *Elaeocarpus* alkaloids, (+)-elaeokanine A and (+)-elaeokanine C is described. The key steps involve an asymmetric Diels-Alder reaction of a chiral sulfinyl dienophile, diastereoselective nucleophilic addition to the acyliminium ion and retro Diels-Alder reaction.

N-Acyliminium ions generated from γ-hydroxy lactams have been recognized as useful intermediates for the synthesis of many alkaloids.[1] Enantiomeric control in nucleophilic additions to iminium ions has been of much interest.[2] Recently we reported an enantioselective synthesis of (+)-indolizidine and (+)-laburnine through *intramolecular* cyclization using an *N*-acyliminium ion **1**, fused with a bicyclo[2.2.1]-heptene moiety.[3] Efforts to explore the generality of this reaction led us to investigate the *intermolecular* nucleophilic addition to the iminium, which should block its concave face from the nucleophilic attack by virtue of the conformationally rigid, tricyclic system, providing an enantioselective route to nitrogen-containing natural products. Elaeokanine A (**2**) and elaeokanine C (**3**)[4] seemed to be suitable target compounds for the embodiment of this subject. In addition, a recent report[4p] on the first synthesis of (+)-**3** prompted us to disclose our own results. Herein, we describe a diastereoselective, intermolecular nucleophilic addition to the iminium intermediate, and its application to an asymmetric synthesis of *Elaeocarpus* alkaloids, (+)-**2** and (+)-**3**.

Scheme 1



The key steps are retrosynthetically illustrated in Scheme 1. A Diels-Alder adduct of a dienophile **4** with cyclopentadiene would generate the acyliminium ion **1**, and the intermolecular addition of a nucleophile (=Nu) could take place in a highly diastereoselective manner. The formation of the 6-membered ring followed by extrusion of cyclopentadiene could afford a Δ^3-pyrrolidinone ring, which can be further transformed into **2** and **3**.



Scheme 2 *Reaction conditions:* a) 3-chloroperoxybenzoic acid, 0 °C, 1.5 h; b) cyclopentadiene, $ZnCl_2$ (1.5 equiv.), -80 °C, 1 h; c) silica-gel chromatography, hexane/AcOEt (4:1); d) 2-(2-bromoethyl)-1,3-dioxolane, NaH, DMF, 0 °C → r.t., 22 h; e) $NaBH_4$, EtOH, reflux, 1 h; f) Sm(II)I_2 (5 mol equiv.), HMPA, t-butyl alcohol, THF, 15 min; g) MeOH, pyridinium *p*-toluenesulfonate, r.t., 12 h; h) 2-(trimethylsilyloxy)-pent-1-ene, BF_3•Et_2O (2 equiv.), CH_2Cl_2, 0 °C → r.t., 3.5 h; i) conc. HCl, r.t., 4 h; j) flash vacuum pyrolysis (435 °C, 0.5 Pa); k) H_2, 5% Pt on alumina, t-butyl alcohol, r.t., 4 h; l) ethylene glycol, $(EtO)_3CH$, *p*-toluenesulfonic acid, reflux, 12 h; m) $LiAlH_4$, THF, reflux, 2 h; 10% H_2SO_4, r.t., 2 h; n) NaOH, EtOH, reflux, 1 h

Our approach starts with the preparation of a chiral sulfinyl maleimide **4** as an efficient dienophile (Scheme 2). It seemed likely that the choice of t-butyldimethylsilyl (TBDMS) group as a protecting group could readily result in the deprotection and in the subsequent incorporation of a functional side chain (*i.e.* propylene acetal unit) on the nitrogen atom. According to the procedure described previously,[3] maleimide **5**

was easily prepared in 64% yield by the addition of 10-mercaptoisoborneol to *N*-TBDMS maleimide[5] followed by chlorination and dehydrochlorination. Exposure of **5** to 3-chloroperoxybenzoic acid afforded the sulfinyl maleimide **4** (R=TMDMS) as a single diastereoisomer (~100% yield).[6] The Diels-Alder reaction of **4** with cyclopentadiene produced the *exo*-sulfinyl adduct **6** as essentially a single product (d.e. >99%). Fortunately, purification of **6** by silica-gel chromatography resulted in desilylation to give the maleimide **7** (80% yield from **5**). The absolute stereochemistry of **7** was unequivocally confirmed by the transformation into the known compound **8**[7] under Mitsunobu conditions. Treatment of **7** with 2-(2-bromoethyl)-1,3-dioxolane and base gave the acetal **9** (93% yield). Regioselective reduction of **9** with $NaBH_4$ (to give **10**, 70% yield) followed by desulfinylation with $Sm(II)I_2$ afforded the γ-hydroxy lactam **11** (92% yield), which was further transformed into **12** (98% yield). Then, we undertook the introduction of carbon chain at C(5) position in **12**. Attempts at intermolecular addition of **12** with 2-(trimethylsilyloxy)-pent-1-ene[4h] in the presence of $TiCl_4$ or $SnCl_4$ were unfruitful, resulting in the cleavage of the dioxolane ring and/or decomposition of starting material. After several attempts, the use of $BF_3 \cdot Et_2O$ was found to be most effective for the addition.[8] The lactam **13** was thus obtained as a single diastereoisomer in 91% yield. The stereochemistry of the newly formed 5-carbon chain adjacent to the C(5) position can be tentatively assigned to be located at β position, assuming that the enol ether should attack the less-hindered convex face of the iminium ion generated from **12**. The tetracyclic lactam **14** was obtained by acid-catalyzed aldol reaction of **13** in 79% yield. Lactam **14** was subjected to flash vacuum pyrolysis. The thermolysis (435 °C, 0.5 Pa) proceeded smoothly to give the pyrrolidinones in a ratio of 3:1, in quantitative yield. The major product **15** was isolated by crystallization of the crude mixture, in 52% yield. The minor product was assumed to be the bridgehead (8*a*) isomer of **15**, which arose from isomerization during the heating.[9] Hydrogenation of **15** over Pt on alumina (to give **16**) followed by protection of the cabonyl group produced the lactam **17** in 91% yield. Reduction of **17** with $LiAlH_4$ and subsequent treatment of the resulting amine with 10% H_2SO_4 finally afforded (+)-**3** {$[\alpha]_D^{26}$ +36.9 (*c* 0.58, $CHCl_3$), lit.[4p] $[\alpha]_D^{23}$ +47 (*c* 0.4, $CHCl_3$)} in 76% yield. The optical purity of the synthetic compound (+)-**3** was estimated as >92% by the ^{19}F NMR analysis of its MTPA [α-methoxy-α-(trifluoromethyl)-phenylacetic acid] ester.[10] (+)-Elaeokanine C (**3**) was transformed into (+)-**2**, $[\alpha]_D^{26}$ +63.0 (*c* 0.93, $CHCl_3$) {lit.[4a] $[\alpha]_D$ +13 (*c* 0.9, $CHCl_3$), lit.[4o] $[\alpha]_D^{22}$ +49 (*c* 0.5, $CHCl_3$), lit.[4p] $[\alpha]_D^{23}$ +47 (*c* 0.31, $CHCl_3$)} in 66% yield, according to the literature method.[4]

In conclusion, we could show that the use of the bicyclo[2.2.1]heptene system resulted in substantial effect on the diastereoselectivity of nucleophilic addition to the pyrrolidinium ion fused with its system, and an easy, synthetic access to a chiral Δ^3-pyrrolidinone ring by the retro Diels-Alder fragmentation. The utility of the methodology was exemplified by a chiral synthesis of (+)-elaeokanine A and (+)-elaeokanine C.

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REFERENCES AND NOTES

1) Speckamp, W.N.; Hiemstra, H. *Tetrahedron* **1985**, *1*, 4367.

2) Chamberlin, A.R.; Chung, J.Y.L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. Irie, K.; Aoe, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633. Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704. Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590. Wanner, K.T.; Kärtner, A.; Wadenstorfer, E. *Heterocycles* **1988**,

27, 2549. Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1988**, *53*, 3865. Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118. Polniaszek, R.P.; Belmont, S.E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. Thaning, M.; Winstrand, L.-G. *J. Org. Chem.* **1990**, *55*, 1406. Polniaszek, R.P.; Belmont, S.E. *J. Org. Chem.* **1990**, *55*, 4688. Polniaszek, R.P.; Belmont, S.E. *J. Org. Chem.* **1991**, *56* , 4868.

3) Arai, Y.; Kontani, T.; Koizumi, T. *Chem. Lett.* **1991**, 2135.

4) For isolation of (+)-2 and (-)-3, see: Hart, N.K.; Johns, S.R.; Lamberton, J.A. *J. Chem. Soc., Chem. Commun.* **1971**, 460.

For racemic syntheses of 2 and 3, see: a) Hart, N.K.; Johns, S.R.; Lamberton, J.A. *Aust. J. Chem.* **1972**, *25*, 817. b) Tufariello, J.J.; Ali, S.A. *Tetrahedron Lett.* **1979**, 4445. c) Howard, A.S.; Gerrans, G.C.; Meerholz, C.A. *Tetrahedron Lett.* **1980**, *21*, 1373. d) Watanabe, T.; Nakashita, Y.; Katayama, S.; Yamauchi, M. *Heterocycles* **1980**, *14*, 1433. e) Khatri, N.A.; Schmitthenner, H.F.; Shringarpure, J.; Weinreb, S.M. *J. Am. Chem. Soc.* **1981**, *103*, 6387. f) Otomasu, H.; Takatsu, N.; Honda, T.; Kametani, T. *Tetrahedron* **1982**, *38*, 2627. g) Overman, L.E.; Malone, T.C.; Meier, G.P. *J. Am. Chem. Soc.* **1983**, *105*, 6993. h) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300. i) Nagasaka, T.; Yamamoto, H.; Hayashi, H.; Hamaguchi, H. Abstracts of papers of 18th Congress of Heterocyclic Chemistry, p 17, October 1986, Fukuoka, Japan. j) Takahata, H.; Yamabe, K.; Suzuki, T.; Yamazaki, T. *Heterocycles* **1986**, *24*, 37. k) Fann, C.; Malone, M.C.; Overman, L.E. *J. Am. Chem.* Soc. **1987**, *109*, 6097. l) Gribble, G.W.; Switzer, F.L.; Soll, R.M. *J. Org. Chem.* **1988**, *53*, 3164. m) Comins, D.L.; Myoung, Y.C. *J. Org. Chem.* **1990**, *55*, 292. n) Taber, D.F.; Hoerner, R.S.; Hagan, M.D. *J. Org. Chem.* **1991**, *56*, 1287.

For chiral syntheses, see: o) Hua, D.Y.; Bharathi, S.N.; Robinson, P.D.; Tsujimoto, A. *J. Org. Chem.* **1990**, *55*, 2128. p) Comins, D.L.; Hong, H. *J. Am. Chem. Soc.* **1991**, *113*, 6672.

5) Matsumoto, A.; Oki, Y.; Horie, A.; Otsu, T. *Chem. Lett.* **1991**, 1141.

6) Diastereoselective oxidation of 2-*exo*-hydroxy-10-bornyl sulfides with 3-chloroperoxybenzoic acid, see: Arai, Y.; Matsui, M.; Koizumi, T. *Synthesis* **1990**, 320.

7) Arai, Y.; Matsui, M.; Koizumi, T.; Shiro, M. *J. Org. Chem.* **1991**, *56*, 1983.

8) In some case, the choice of Lewis acid is crucial for the completion of the reaction and high diastereoselectivity, see: Kraus, G.A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134.

9) It is known that Δ^3-pyrrolin-2-ones are thermally unstable, and undergo an irreversible isomerization to give the corresponding Δ^4-isomers. see: Baker, J.T.; Sifniades, S. *J. Org. Chem.* **1979**, *44*, 2798.

10) In the ^{19}F NMR spectrum. the esters obtained by the reaction of (+)-MTPACl with (±)-3 (prepared from (±)-11) were resolved to a pair of singlets at -71.75 and -71.80 ppm ($CFCl_3$ as internal standard). The MTPA ester of (+)-2 showed at -71.80 ppm. The peak of the corresponding diastereoisomeric ester (< 4%) was observed at -71.75 ppm.