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Spotlight 178

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Nazarov Reagent: A Novel Reagent for the Synthesis of Natural Products

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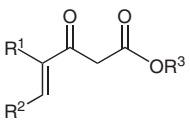
Introduction

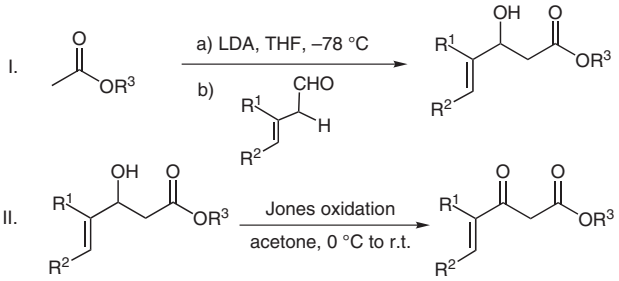
The Nazarov reagent (ethyl-3-oxo-4-pentenoate) is frequently used as an annulating agent in many important reactions. Annulation reaction comprises Michael and Aldol condensations and is used for the construction of molecular scaffolds which constitute the core structure of many natural products. This reagent generates different classes of natural products, mainly steroids, cardenolides, terpenoids, antibiotics and alkaloids. Modified Nazarov reagents have been used for generating diverse chemical scaffolds.[1]



$R^1 = R^2$ = Me or H
R^1, R^2 = Part of any cyclic system
R^1 = H, R^2 = Me
R^1 = Br, R^2 = H
R^3 = -CO_2Me, -CO_2Et, -CO_2*t*-Bu, -SOPh, -CO_2All

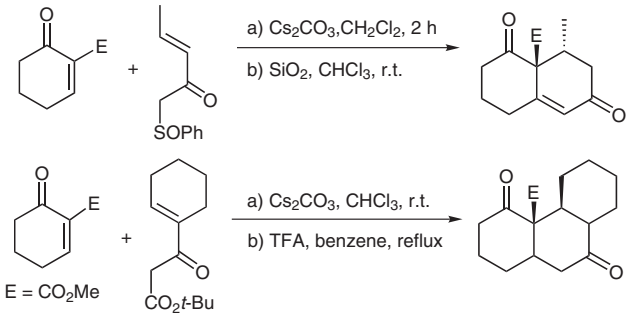
Preparation

The Nazarov reagent can be prepared by the following method. These substituted Nazarov reagents are specific for the generation of different classes of natural products.[2]



Abstracts

(A) The 1-phenylsulfinyl and sulfonyl analogues of the Nazarov reagent are used for the highly stereoselective double Michael cyclization.[3a] This reagent gives the *cis*-decalin with high yield while other methods result in the generation of either *trans*-decalin or a considerable decrease in stereoselectivity.[3b]



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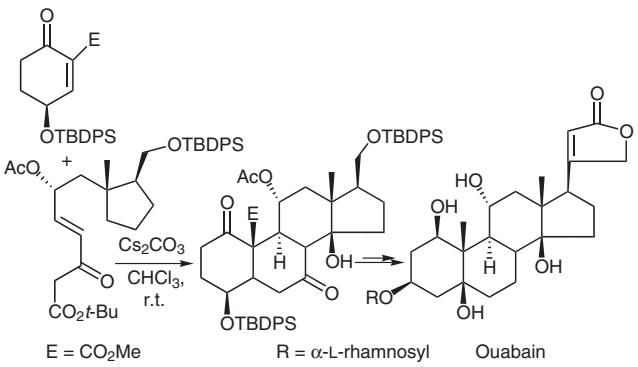
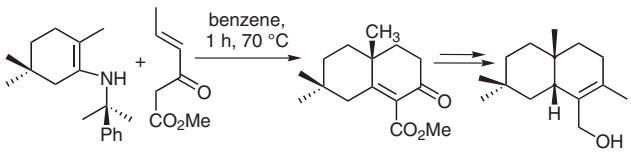
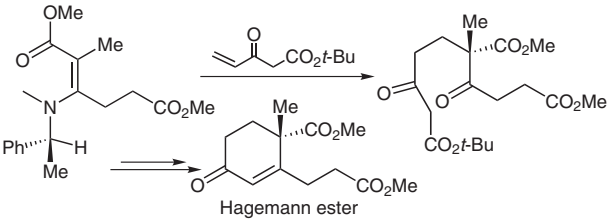
(B) The new bicyclic Nazarov reagent is used for the convergent and expedient synthesis of naturally occurring cardioactive steroids.[4a] One such example is the synthesis of natural product ouabain isolated from the leaves of the plant *Digitalis*, which has potential for treating hypertension as well as congestive heart failure.[4b] This reagent was prepared from Hajos–Parrish ketone in quantitative yield.[4c]



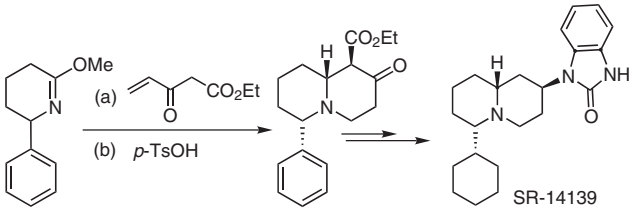
(C) Synthesis of a precursor of (+)-preoleanatetraene has been accomplished using the Nazarov reagent and a chiral amine.[5a] The Nazarov reagent can also be used for the synthesis of sesquiterpenes[5b] and pentacyclic triterpenes.[5c]



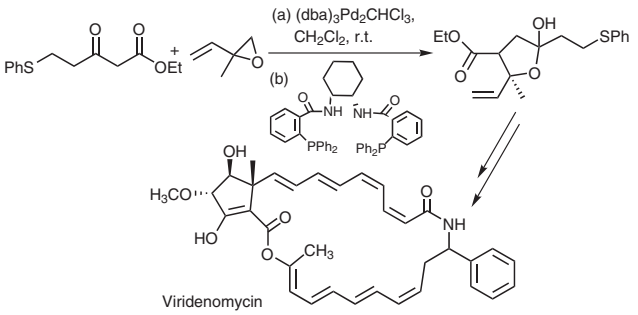
(D) Hagemann's ester can be synthesized using Nazarov reagent and enamino ester with 95% ee.[6]



(E) An efficient synthesis of SR-14139, having opioid-receptor-like activity has been achieved by the Nazarov reagent.[7]



(F) The β-thio derivative of the Nazarov reagent has been exploited for the synthesis of the cyclopentyl core of antitumor antibiotic viridenomycin.[8]



References

(1) Bodalski, R.; Pietrusiewicz, K. M.; Monkiewicz, J.; Koszuk, J. *Tetrahedron Lett.* **1980**, *21*, 2287.

(2) (a) Streiber, J.; Zibuck, R. *Org. Synth.* **1993**, *71*, 236. (b) Gaul, M. D.; Boeckman, R. K. Jr. *Org. Synth.* **1998**, *9*, 432.

(3) (a) Spino, C.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3969. (b) Lepage, O.; Stone, C.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 1091.

(4) (a) Chapdelaine, D.; Belzile, J.; Deslongchamps, P. *J. Org.Chem.* **2002**, *67*, 5669. (b) Yang, Z.; Shannon, D.; Truong, V. L.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 4693. (c) Hajos, Z.; Parrish, D. R. *Org. Synth.* **1985**, *63*, 26.

(5) (a) Barrero, A. F.; Arseniyadis, S.; del Moral, J. F. Q.; Herrador, M. M.; Rosellón, A. *Synlett* **2005**, 789. (b) Beauhaire, J.; Ducrot, P.-H. *Tetrahedron Lett.* **2002**, *43*, 4637. (c) Rouillard, A.; Deslongchamps, P. *Tetrahedron* **2002**, *58*, 6555.

(6) Gassama, A.; d'Angelo, J.; Cavé, C.; Mahuteau, J.; Riche, C. *Eur. J. Org. Chem.* **2000**, 3165.

(7) Jong, L.; Zaveri, N.; Toll, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 181.

(8) Trost, B. M.; Jiang, C. *Org. Lett.* **2003**, *5*, 1563.