

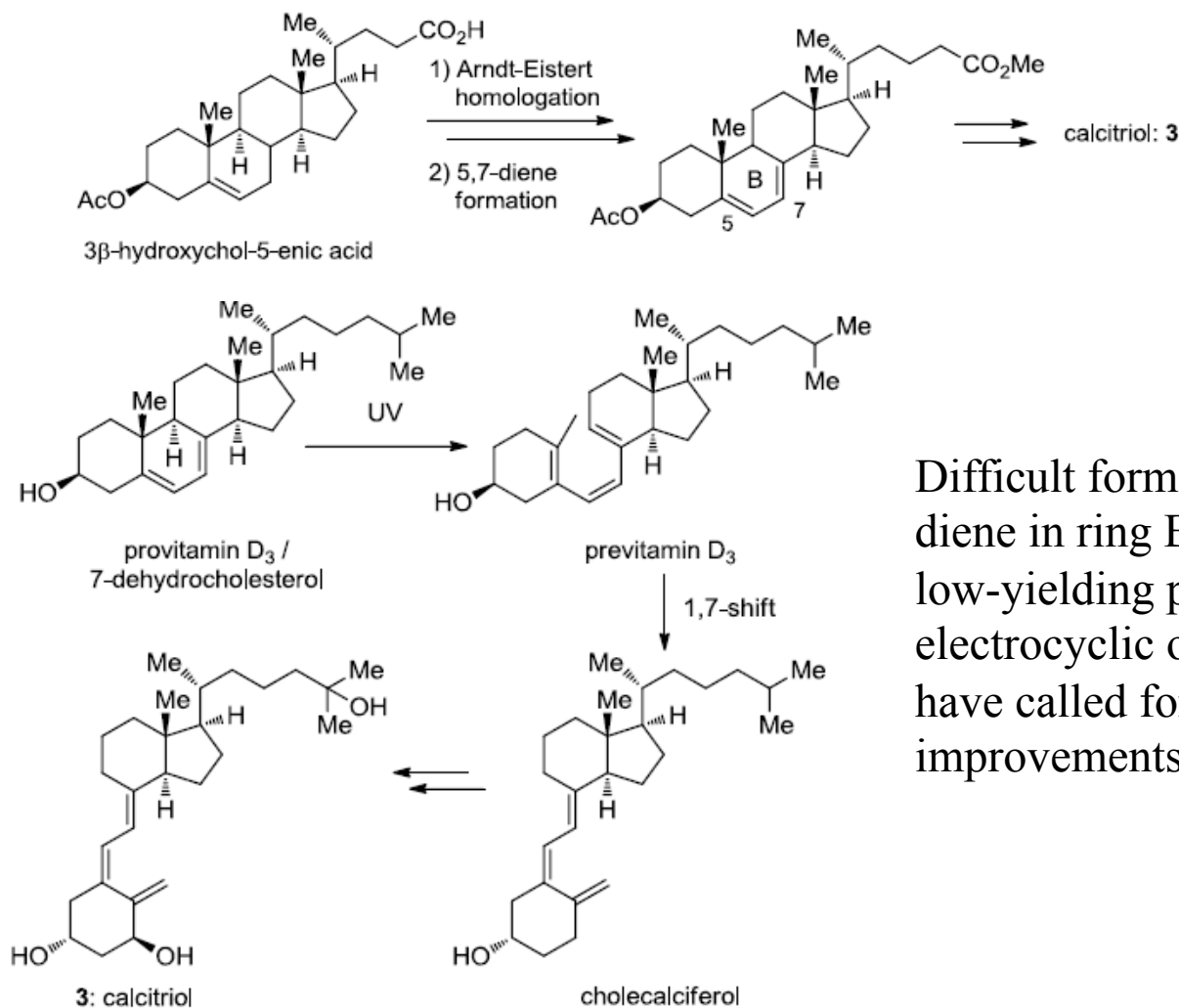
Industrial application of the Diels-Alder reaction

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Overview of the use of [4+2] cycloadditions for the manufacture of active **pharmaceutical ingredients**, **agrochemicals**, **flavors** , and **fragrances** on a scale above 1 kg.

1. Industrial-scale synthesis of Vitamin D and its analogues

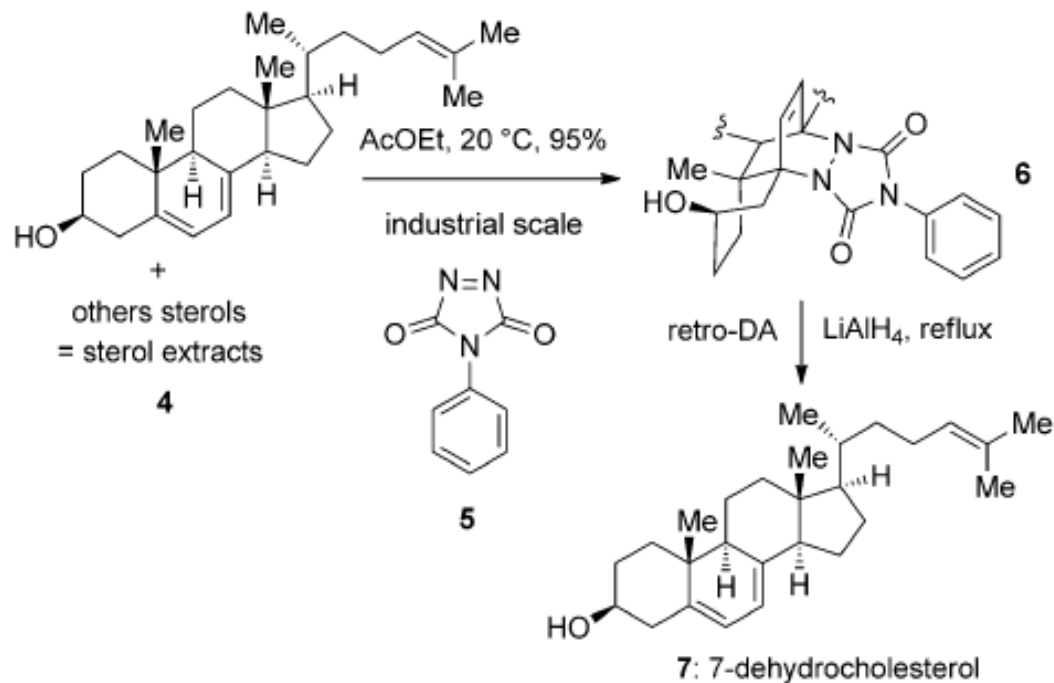
- First produced as a biomimetic process established at Upjohn in 1969:



Difficult formation of the 5,7-diene in ring B (ca. 20%) and low-yielding photochemical electrocyclic opening of the ring have called for process improvements.

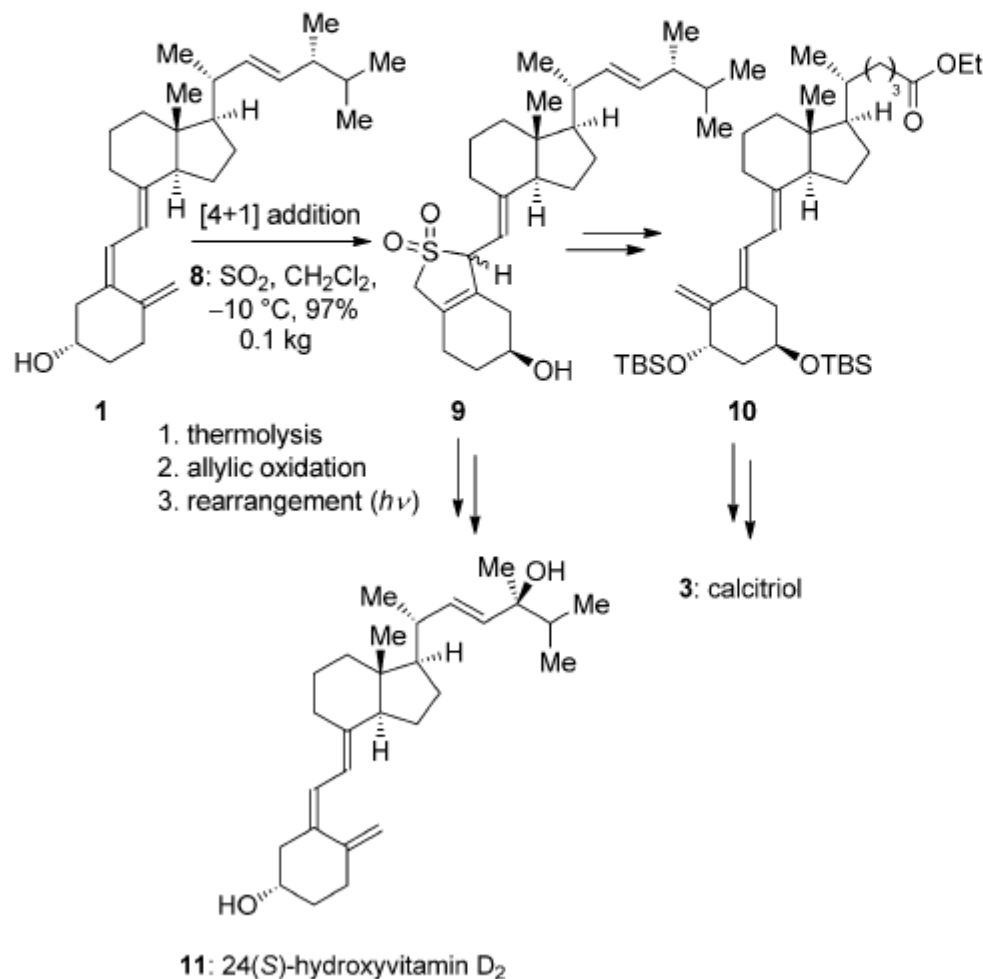
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- Industrial isolation of 7-dehydrocholesterol starting from yeast fermentation products:



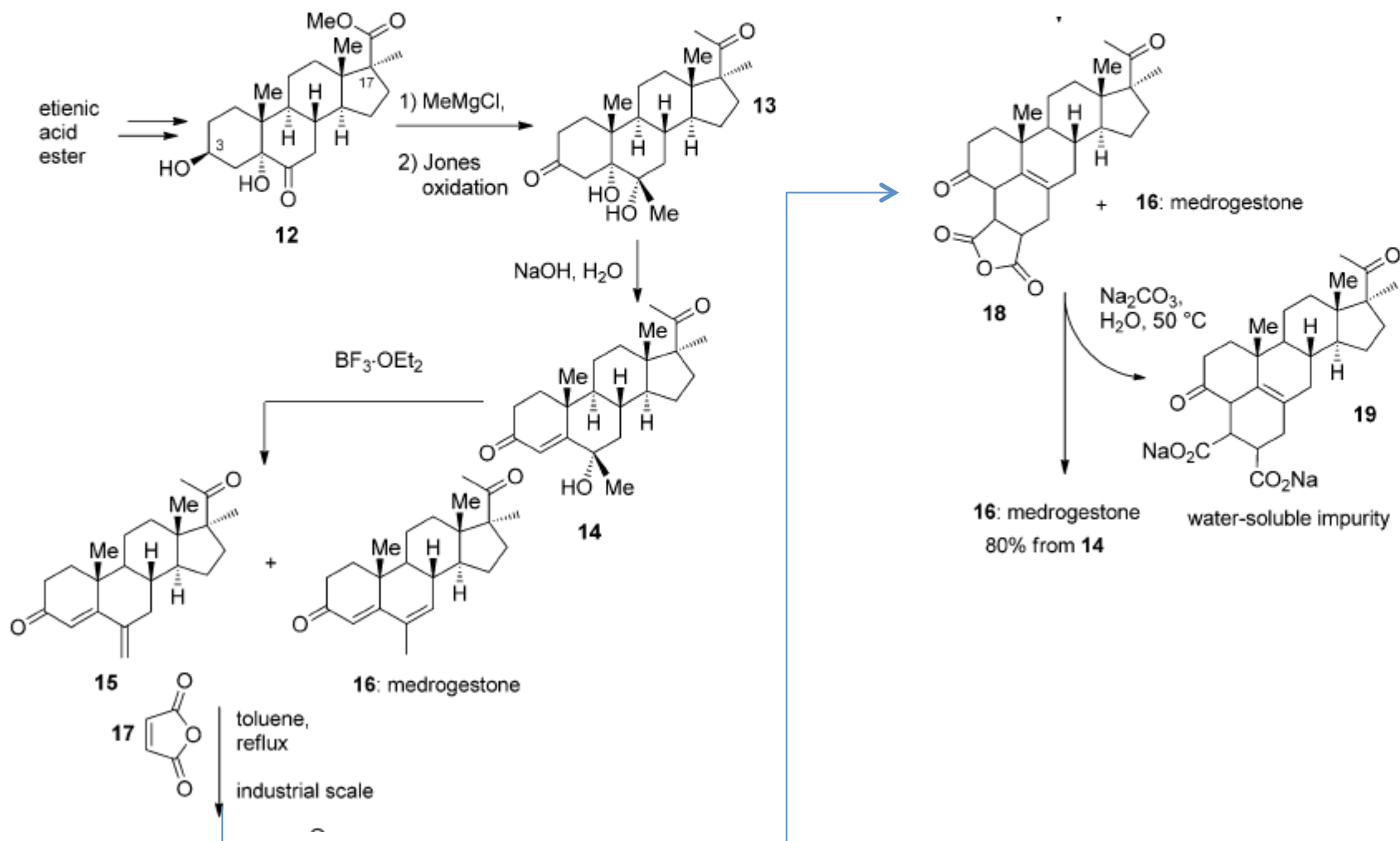
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- The DA/retro-DA strategy was extended to the use of sulfur dioxide by Barton, Hesse, and co-workers:



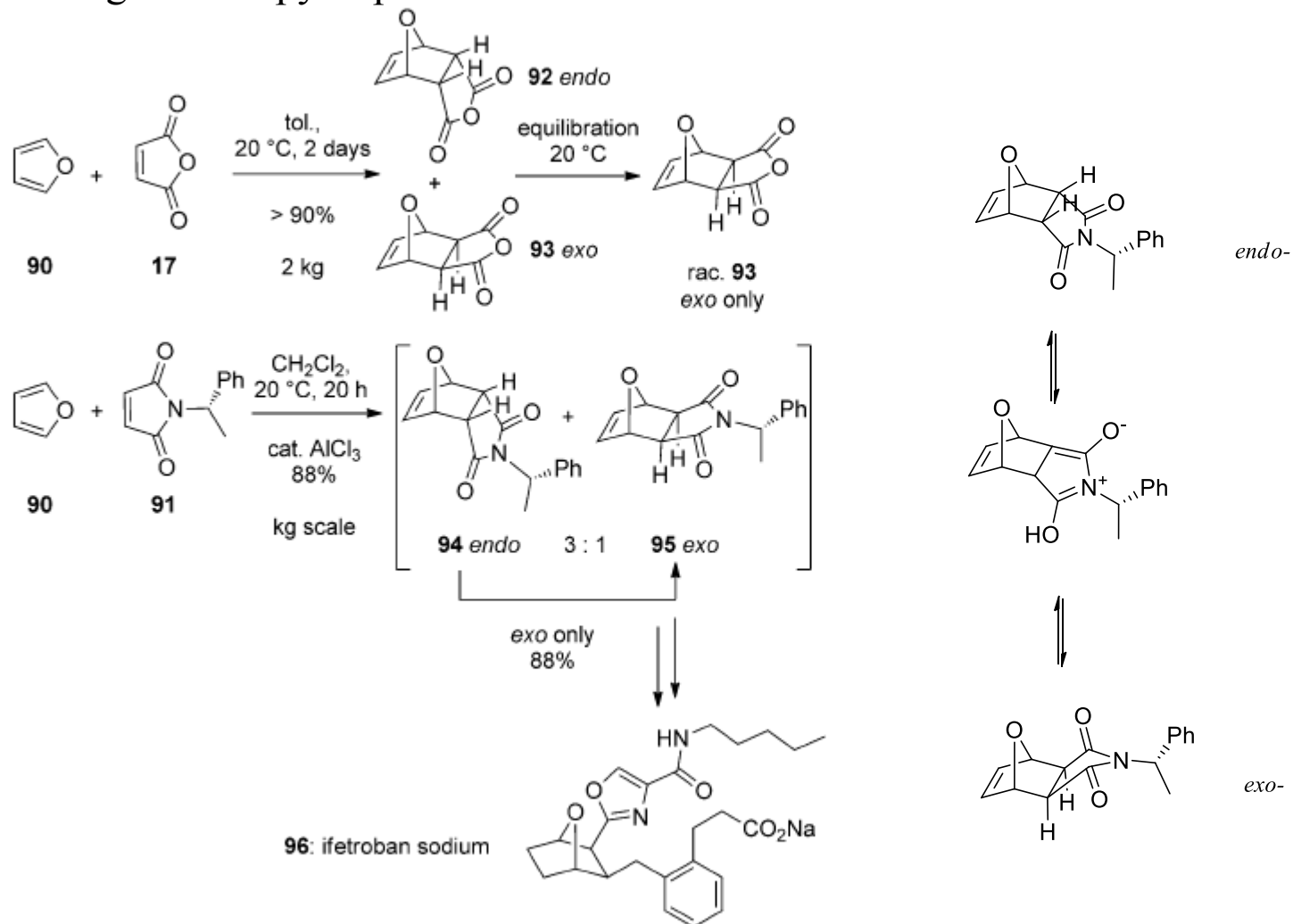
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- The large-scale synthesis of medrogestone-another illustration of the industrial purification of a desired compound after a sequential DA/retro-DA reaction:



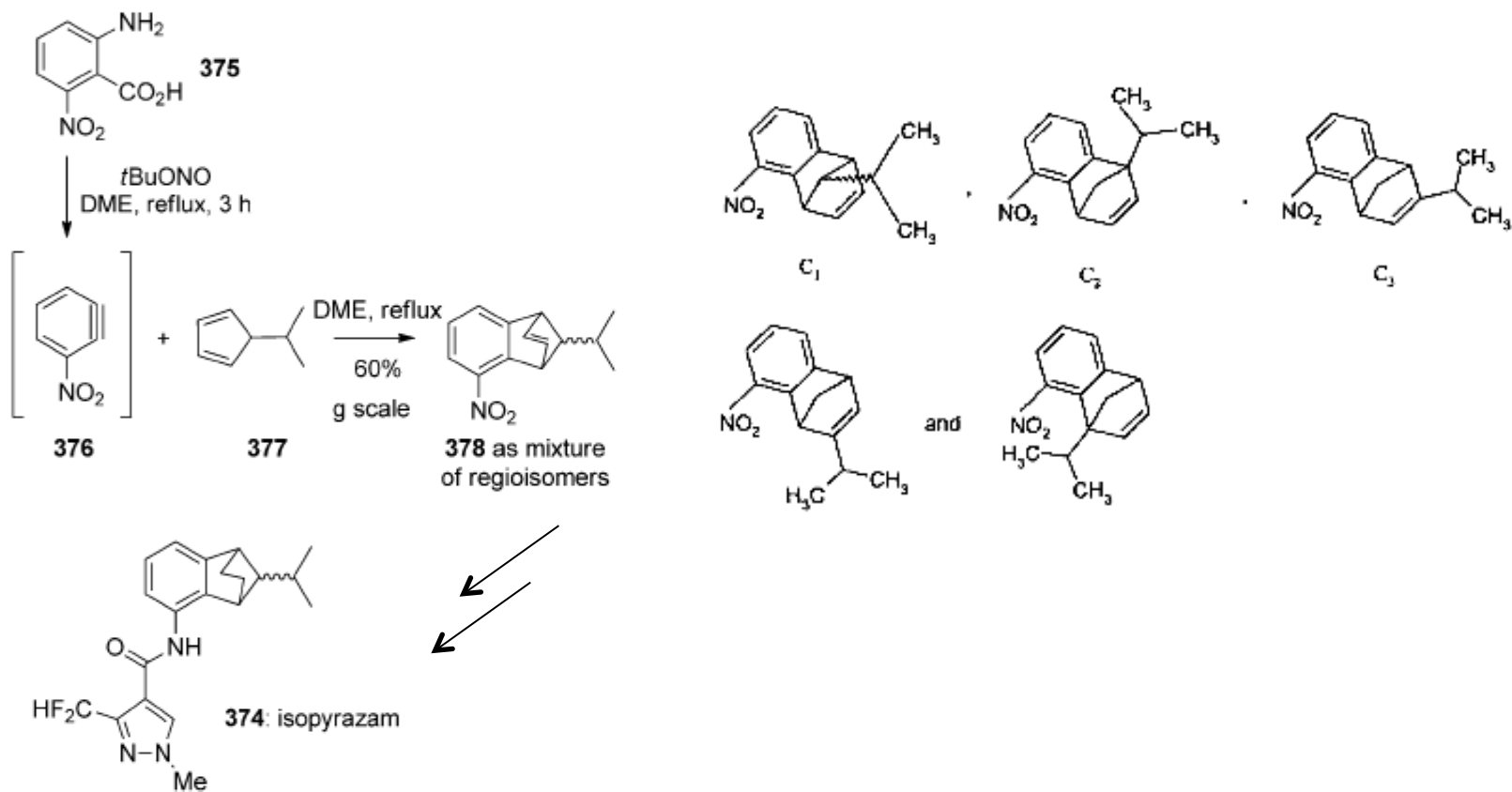
2. Synthesis of Ifetroban sodium: an example of furan as diene

- Ifetroban sodium was a selective thromboxane receptor antagonist investigated as an antiplatelet agent therapy in phase II clinical trials at BMS.



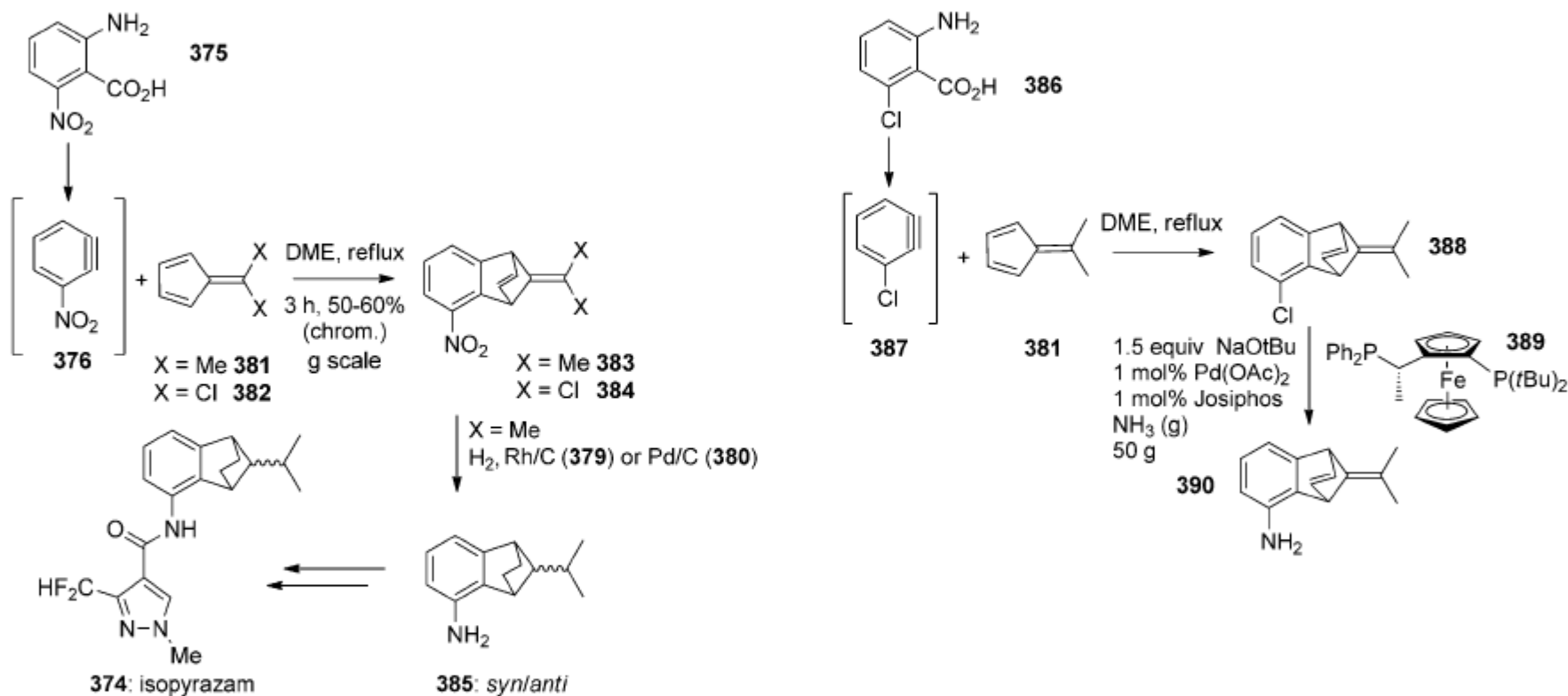
3. Synthesis of Isopyrazam: an example of benzyne as dienophiles

• Isopyrazam (**374**) was registered in the UK in 2010 by Syngenta as a new cereal fungicide and is sold as a mixture of *syn* and *anti* diastereoisomers. This active substance was selected from a series of active substances belonging to the class of (difluoromethyl)pyrazole compounds.



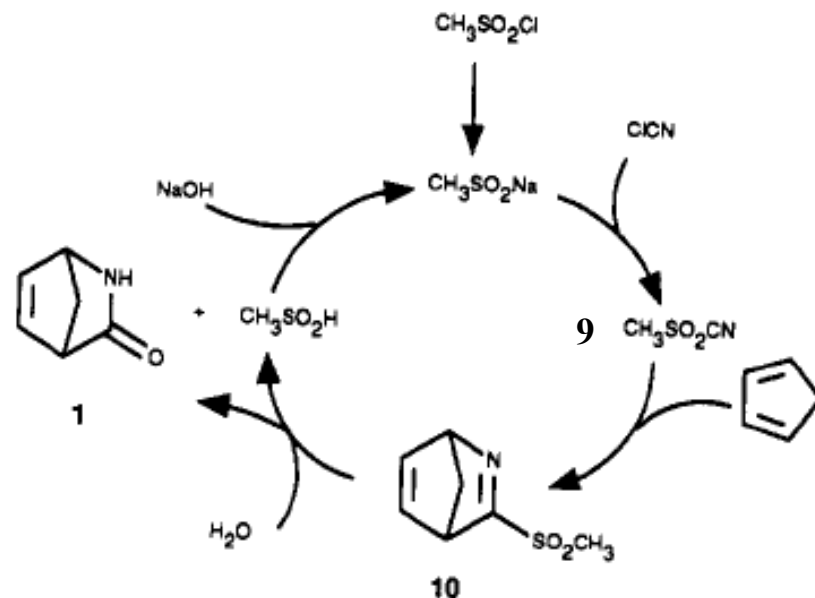
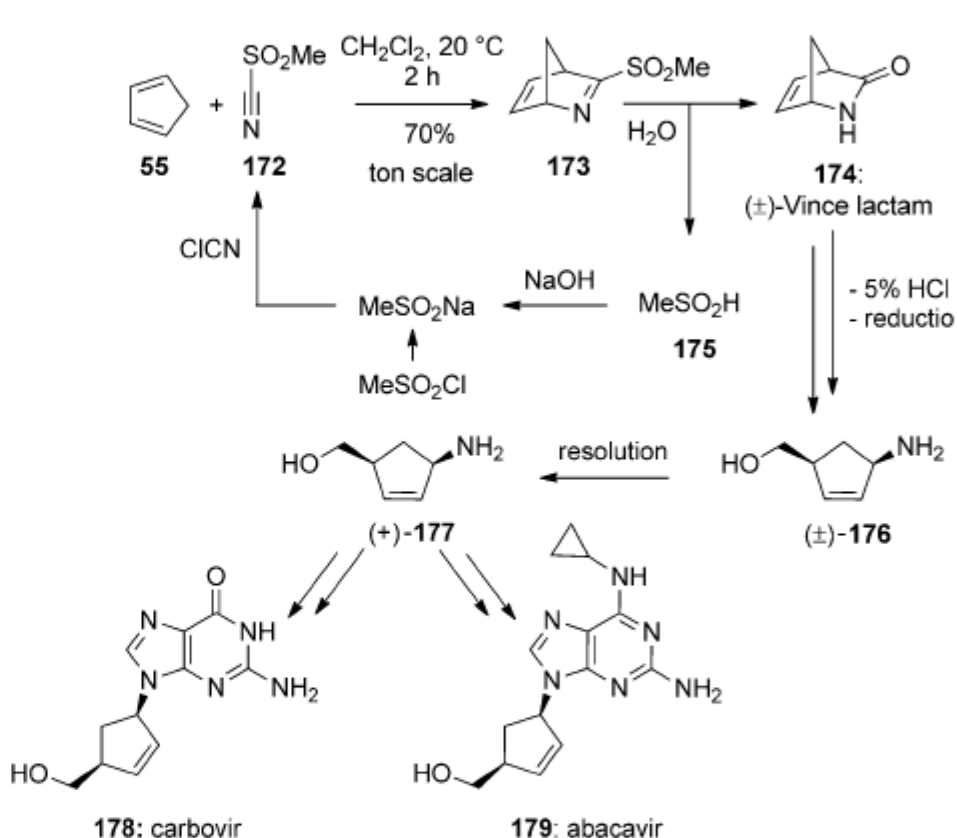
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4. Synthesis of Abacavir: an example of hetero-DA reactions

- Abacavir (**179**) is a reverse transcriptase inhibitor that was launched in 1999 by GSK for the oral treatment of HIV infection.



G. J. Griffiths, F. E. Previdoli, *J. Org. Chem.* **1993**, 58, 6129.

E. D. Pinheiro, O. A. C. Antunes, J. M. D. Fortunak, *Antiviral Res.* **2008**, 79, 143.