

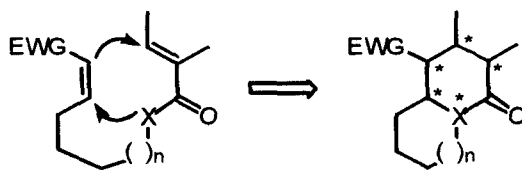
Development of Cascade Reactions and Their Application to Efficient Synthesis of Biologically Active Natural Products

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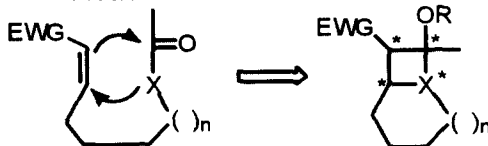
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A cascade reaction forming multiple bonds in a stereo- and regioselective manner by one reaction procedure is one of the most ideal processes in organic synthesis. We have investigated cascade reactions on which electrons move as boomerang between functional groups in the same molecule. As the result, two types of cascade reactions, the intramolecular double Michael reaction and the intramolecular Michael-aldol reaction, have been developed. Polycyclic systems fused to six-membered ring are effectively constructed by the former, while the latter leads to the facile formation of polycycles fused to four-membered ring.

Intramolecular Double Michael Reaction

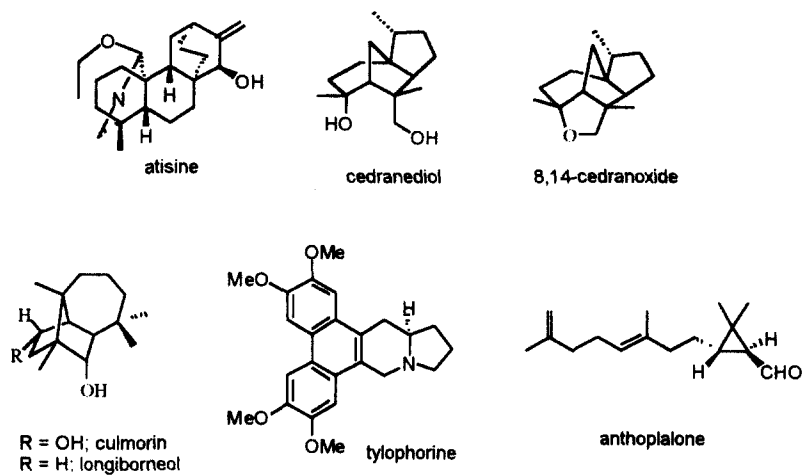


Intramolecular Michael-Aldol Reaction

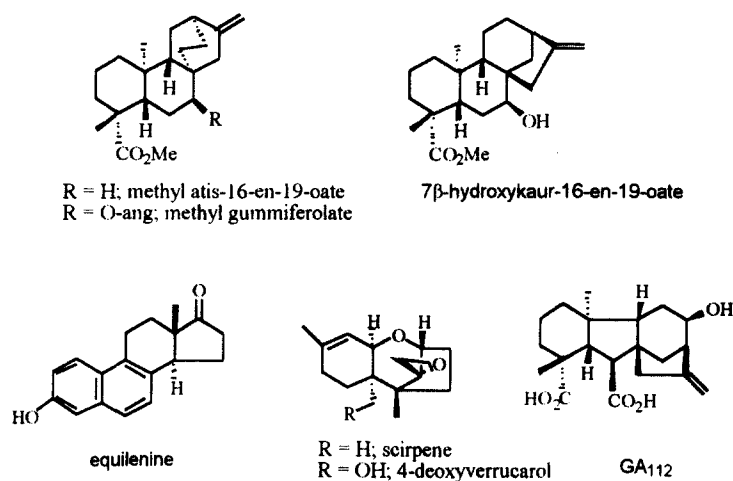


The cascade reactions are carried out under five different reaction conditions, (A) $\text{LiN}(\text{TMS})_2$; (B) $\text{TMSCl-ZnCl}_2\text{-Et}_3\text{N}$; (C) $\text{TBSOTf-Et}_3\text{N}$; (D) $\text{TMSI-(TMS)}_2\text{NH}$; (E) $\text{Bu}_2\text{BOTf-(TMS)}_2\text{NH}$. A number of continuous stereogenic centers are concurrently built by above reactions. The characteristic feature of these reactions

is that multiple bond formation leading to polycyclic ring construction can be achieved under mild reaction conditions with a high stereoselectivity and a complete regioselectivity. Applications of these methodologies led to total syntheses of natural products, atisine, cedranediol,¹ 8,14-cedranoxide,¹ culmorin,² longiborneol,² tylophorine, anthoplalone and so on.



We have further studied the extension of cascade reactions under radical or transition metal catalyzed conditions. Application of homoallyl-homoallyl radical rearrangement accomplished syntheses of methyl atis-16-en-19-oate,³ methyl gummiferolate,⁴ and methyl 7 β -hydroxykaur-16-en-18-oate. Total syntheses of equilenin,⁵ scirpene,⁶ 4-deoxyverrucarol,⁷ and GA₁₁₂⁸ were achieved via palladium catalyzed reactions. Further topics would be also discussed.



References

1. Ihara, M.; Makita, K.; Takasu, K. *J. Org. Chem.* **1999**, *64*, 1259-1264.
2. Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. *Org. Lett.* **1999**, *1*, 391-393; *J. Org. Chem.* **2000**, *65*, 4112-4119.
3. Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916-4925.
4. Toyota, M.; Yokota, M.; Ihara, M. *Org. Lett.* **1999**, *1*, 1627-1629.
5. Nemoto, H.; Yoshida, M.; Fukumoto, K.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 909-910.
6. Nemoto, H.; Takahashi, E.; Ihara, M. *Org. Lett.* **1999**, *1*, 517-519.
7. Miyata, J.; Nemoto, H.; Ihara, M. *J. Org. Chem.* **1999**, *65*, 504-512.
8. Toyota, M., Odashima, T., Wada, T., Ihara, M. *J. Am. Chem. Soc.* **2000**, in press