DEVELOPMENT AND APPLICATIONS OF NEW YLID CHEMISTRY

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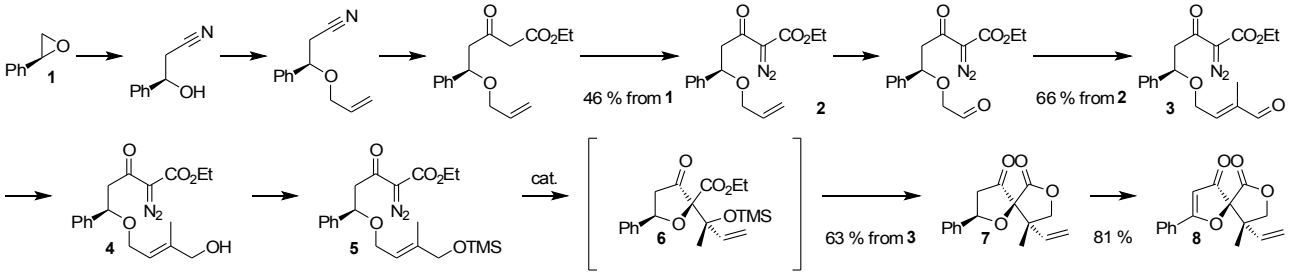
Using new oxonium ylid formation [2,3] sigmatropic rearrangement chemistry we developed a ten-step asymmetric synthesis of hyperolactone C (**8**) from (*S*)-styrene oxide (**1**) (Scheme 1).[1] Hyperolactone C (**8**) was originally isolated from the leaves and stems of *Hypericum chinese L.* (1995)[2] as a part of a small family of related lactones. Hyperolactone C and *ent*-zingiberene are precursors of biyouyanagin A,[3] a new *anti*-HIV agent.[4]



Scheme 1: Synthesis of hyperolactone C (**8**) from (*S*)-styrene oxide (**1**).

This work built upon an earlier racemic Hodgson synthesis.[5] First of all a new synthetic pathway to chiral diazo ether **2** from **1** was developed. Since styrene oxide along with related epoxides are commercially available in both enantiomeric forms (via kinetic resolution), the method could be considered as more general entry to chiral diazo ethers. Also, a series of chiral auxiliaries (thiazolidine-2-thiones) in combination with Masamune homologation was systematically examined in the synthesis of **2**, but was shown to be a less efficient strategy.

We established that distabilized diazo compounds like **2** are stable enough to survive ozonolysis to form an aldehyde that underwent olefination with a stabilized Wittig reagent to give enone **3**. By this approach a previously unreliable cross-metathesis[5] was replaced in the current synthesis of enone **3**.

Lactone **7** was prepared from enone **3** by a four-step sequence, with only one chromatographic purification being required. The sequence was: reduction, silylation, Rh_2-cat. oxonium ylid formation–rearrangement and then acid cat. desilylation–lactonization. Lactone **7** was formed preferentially alongside the other three possible diastereomers. Finally, (–)-hyperolactone C (**8**) was prepared by one-pot silylation–DDQ oxidation of lactone **7**, under mild conditions.

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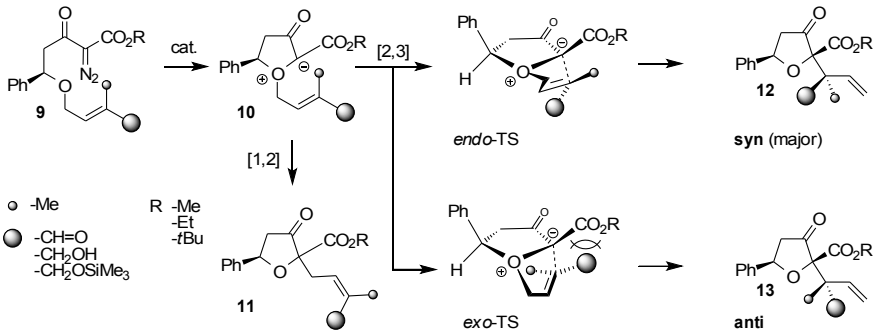
1 D. M. Hodgson, S. Man, *Chem. Eur. J.* **2011**, *17*, 9731. http://dx.doi.org/doi:10.1002/chem.201101082
2 Aramaki Y., Chiba K., Tada M., *Phytochemistry* **1995**, *38*, 1419.
3 Nicolaou K. C., Sarlah D., Shaw D. M., *Angew. Chem. Int. Ed.* **2007**, *46*, 4708.
4 Tanaka N., Okasaka M., Ishimaru Y., Takaishi Y., Sato M., Okamoto M., Oshikawa T., Ahmed S. U., Consentino L. M., Lee K.-H., *Org. Lett.* **2005**, *7*, 2997.
5 Hodgson D. M., Angrish D., Erickson S. P., Kloesges J., Lee C. H., *Org. Lett.* **2008**, *10*, 5553.

It is important to note that all of the diazo compounds **3**,[5] **4** and **5** underwent oxonium ylid formation–rearrangement and could be used for the synthesis of lactone **7** as the major product; however, using silyloxy ester **5** was identified as the optimal route.

The key oxonium ylid formation–rearrangement step (Scheme 2), could proceed by four possible pathways, forming four diastereomers with two new quaternary stereocenters, **12** being the major and desired. Rh. cat. "decomposition" of diazo compound **9** gives ylid **10** followed by [2,3] sigmatropic rearrangement preferentially via *endo*-TS. Also, the Ph group on the furanone ring could be in two relative orientations with respect to ester group with preferable *cis* orientation.

No effect of catalyst ($Rh_2(OAc)_4$ or $Rh_2(TFA)_4$) on the selectivity of reaction was observed. Reactant **9**, bearing a CH=O group, showed high preference for *cis* orientation (>90 %, Ph – CO_2R), but relatively low preference for *endo*-TSs (~80 %) and practically no effect of R ester group size. Also, a significant quantity (~25 %) of side product **11**, probably formed via [1,2] shift, was observed.

On the other hand, hydroxy and silyloxy derivatives **9** gave only products of [2,3] rearrangement and showed high endo selectivity (>93 %). Interesting, an increase in face selectivity with a decrease in R size and with OH protection by TMS (52 – 74 % for OH and 74 – 85 % for OTMS) was observed.



Scheme 2: Mechanism of oxonium ylid formation–rearangement.

Conclusion:

We developed a new asymmetric synthesis of the structurally interesting synthetic target – hyperolactone C (**8**). By detailed study of the behavior of diazo compounds **9**, we identified the optimal substrate (OTMS derivative) for oxonium ylid formation–rearrangement. That new knowledge was subsequently utilized for a new and more general synthetic strategy to hyperolactones, based on diazosubstrates, but the strategy is still under development.