Total Synthesis

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Protecting-Group-Free Total Syntheses: A Challenging Approach

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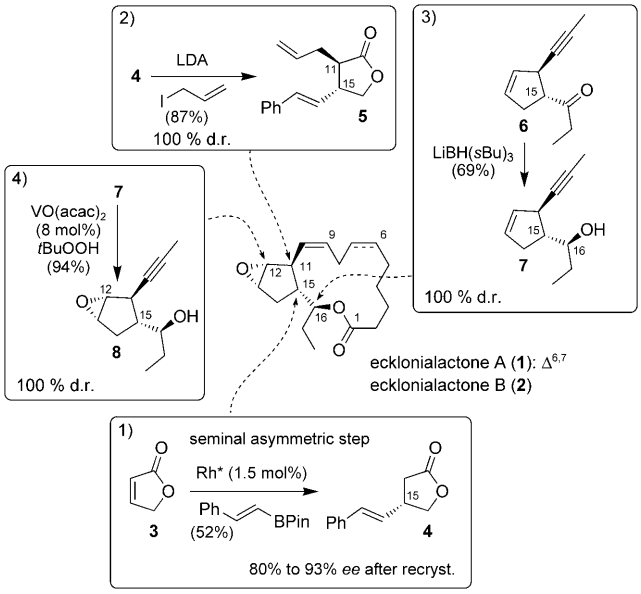
Multistep synthesis, and in particular, total synthesis of natural product is a refined scientific activity.[1] After two centuries of breakthroughs, organic chemistry has become a "predictive science" just as, for example, nuclear physic. However, total synthesis remains an activity so difficult that designing a totally reliable retrosynthetic plan remains almost impossible. Over many decades, the objectives of total synthesis were solely to get higher yields, higher chemo- and stereoselectivity, and higher convergence. Nevertheless, this led to much innovative success. In the mid 90s, a new philosophy arose for multistep synthesis that took new constrains into account: step economy, atom economy,[2] and redox economy. This put stimulating pressure on chemists' inventiveness and led to even more aesthetic and straightforward syntheses. Pushed forward by the demands of our society, chemical science must now go one more step toward maturity by taking into account ecologic considerations. This means that chemists must now design retrosynthetic plans incorporating protective-group-free strategies,[3] thus adding a further refinement to the already complicated art of total synthesis. Thanks to tremendous advances recently accomplished in organic chemistry, and particularly in catalyzed processes, this refinement is now a reachable aim. Thus, many new kinds of catalyst are now described, and they are endowed with always higher selectivity, functional group tolerance, thus allowing milder conditions and accomplishing ewactions hitherto unprecedented. Chemistry catalogues list many of them, and these catalysts involve almost all the elements of the periodic table.

However, performing a total synthesis without any protective groups remains delicate and requires a strong expertise in organic chemistry. Therefore, for the moment it seems that only the medium-sized molecules, bearing only a dozen functionalities and even less asymmetric centers, can be targeted with success. The protecting-group-free total synthesis of the ecklonialactones, achieved by the research group of Fürstner, is a recent and striking example.[4] This synthesis deals with small-sized targets: ecklonialactones A (**1**) and B (**2**) which are macrolactonic oxylipins of marine origin containing five stereogenic centers and without remarkable biological activities. Nevertheless, this kind of target is particularly interesting since only few examples of protecting-group-free syntheses of polyketides have been reported to date, while protecting-group-free syntheses of alkaloids are more represented.[3]

In this concise total synthesis it is noteworthy that only one enantioselective reaction was used. It allowed installation of the stereogenic center at C15, which is an asymmetry that was then transferred to the other centers through substrate-directed enantioselective transformations.[5] This kind of strategy is well-known and powerful, and meets economic and ecological concerns. Scheme 1 summarizes the installations of the asymmetric centers through this strategy: 1) C15 was controlled by the sole enantioselective reaction of this synthesis: a rhodium-catalyzed asymmetric 1,4-addition of a vinyl borane in a butenolide that set the starting point for the control of all the others asymmetric centers of the target. Recrystallization was however required to increase the moderate enantiomeric excess of this step. 2) A classical



Scheme 1. Instrumental role played by substrate-directed reactions to set asymmetric centers in a highly economic fashion. acac = acetylacetonate, LDA = lithium diisopropylamide, pin = pinacol.

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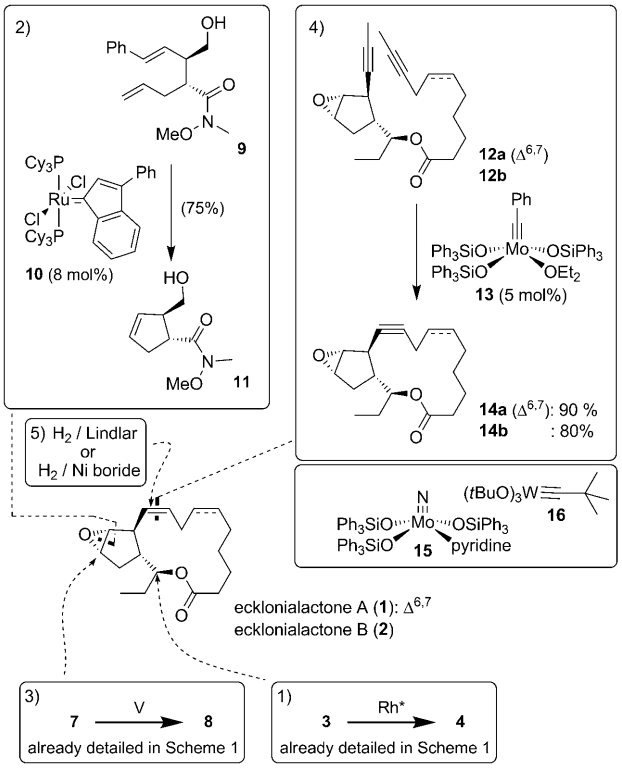
diastereoselective allylation of enolate was used to control center C11. 3) The asymmetric alcohol function at C16 was obtained by diastereoselective reduction of the corresponding ketone by L-Selectride. 4) The epoxide function at C12 was installed through a vanadium-catalyzed epoxydation directed by the proximal hydroxy group at C16, indeed transferring the asymmetry of the seminal stereogenic center at C15.

One must also notice that this thirteen-step total synthesis relies on five catalyzed reactions (Scheme 2). Those steps are all based on transition metals: rhodium, ruthenium, vanadium, molybdenum, and nickel or palladium. The rhodium-catalyzed 1,4-addition used to secure the seminal stereogenic center at C15 (Scheme 2, frame 1) and the vanadium-catalyzed epoxidation (Scheme 2, frame 3) have already been mentioned above. Ring-closing metathesis (RCM) reactions are the two others important catalyzed steps of this total synthesis. First, a classic RCM of alkenes yielded cyclopentene **11** by treatment of diene **9** with ruthenium carbene **10** (Scheme 2, frame 2). Then, a more rarely utilized reaction, the RCM of alkynes[6] that involved the new molybdenum complex **13**, allowed the closure of the 14-membered macrolactonic ring of **14a** and **14b** from diynes **12a** and **12b**, respectively (Scheme 2, frame 4). Metathesis reactions have proved so powerful that they have led chemists to dare attempt new retrosynthetic disconnections through alkene and alkyne groups, which are now no longer regarded as unreactive functions.

This true revolution in organic chemistry eventually led, in 2005, to the Nobel Prize in Chemistry. Thus Chauvin,[7] who discovered the mechanism, shared this award with Schrock[8] and Grubbs,[9] who both designed well-defined and highly efficient catalysts. Numerous ruthenium- and molybdenum-based catalysts for RCM of alkenes have been described since, and many are commercially available. It was Schrock who discovered well-defined catalysts, such as $[W(CCMe_3)(POEt_3)Cl_3]$,[10] that led the way for the metathesis of alkynes. Being a Lewis acid, this kind of catalyst is unfortunately very sensitive to water, oxygen, and even to nitrogen! Correlatively, those catalysts of course are poorly tolerant to the classical functional groups of organic chemistry, therefore imposing the use of protective groups. These disadvantages precluded the use of alkyne metathesis in total synthesis for years, thus making the discovery of new catalysts an obvious challenge which has been taken up by Fürstner and coworkers. Thus, the reactivity of molybdenum catalysts used in alkyne metathesis was tuned by introducing new ligands; this resulted in far less air-sensitive catalysts, which even became tolerant to the various functional groups usually present in natural products, while remaining selectively unreactive with alkenes. In this way, the new molybdenum catalyst **13** was sufficiently less Lewis acidic compared to its predecessors **15** and **16**, so it cleanly delivered macrolactones **14a** and **14b**, and this despite the unusually high propensity of their oxirane function for ring opening. The last step of the syntheses of **1** and **2** were palladium- or nickel-catalyzed semihydrogenations of the triple bound leading to the desired *Z* alkene at C9.

The total synthesis commented upon here is an example of what henceforth should be the objective for all total syntheses, and for multistep syntheses in general. This example demonstrates that the challenges mentioned in the introduction are reachable when one sets retrosynthetic plans cleverly—by allying older synthesis strategies, such as substrate-directed reactions, with the bond disconnections that are now possible using the new catalysts. Chemists are now waiting to see the accomplishment of other total syntheses which follow this approach and that deal with larger, more complex, and more biologically interesting targets. This challenge, a deliberately chosen one, will eventually lead to the discovery of new reactions and will likely trigger great innovations in organic chemistry.



Scheme 2. Using selective and tolerant catalysts for greater economic synthesis. Cy = cyclohexyl.

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