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All-carbon quaternary centers in natural products and medicinal chemistry: recent advances

Taotao Ling, Fatima Rivas *

Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

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1. Introduction

A remaining challenge in the synthetic chemistry field is formation of all-carbon quaternary centers, a feature found in many natural products, particularly in spirocycle systems.[1] Methodologies that can readily generate asymmetric quaternary centers stereoselectively are highly desirable. This research area offers an untapped opportunity to discover new chemical reactivity to access novel chemical matter to treat human disease. Natural products (NPs) are a rich source of therapeutic leads due to their diverse chemical scaffolds, which often contain all-carbon quaternary stereocenter. In fact, currently over 50% of all drugs in clinical use are derived from NPs.[1] Although, the use of small molecule has become routine in drug discovery programs, natural products synthesis remains an essential component of basic research and continues to contribute to the medicinal chemistry programs.[1]

This brief report will highlight recent advancements in the syntheses of all carbon quaternary centers, particularly spirocycle formation and a few applications towards compounds of medicinal value.

Herein, we have surveyed the most recent advances (2010–2015) to generate all carbon quaternary centers, other

* Corresponding author. Fax: +1 901 595 571; e-mail address: fatima.rivas@stjude.org (F. Rivas).

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relevant efforts not included have been described in detailed by Overman, Marek, Aggarwal, and Stoltz among others.[2–6] The review also highlights a selected number of total syntheses of natural products containing all-carbon quaternary spirocenters, and promising medicinal properties, illustrating how the natural product field continues to play a significant role in the drug discovery process.

2. General principles

Classical approaches to generate all carbon quaternary centers from simple synthons (Fig. 1) include i) alkylation reactions, ii) allylations, iii) conjugate additions, iv) rearrangement reactions, v) metal mediated reactions, and variations of these reactions.[2] These chemical processes are well described in the literature.[2–4,8] The current state of organic chemistry strongly prefers that molecules are prepared enantiomerically pure, and that their synthetic strategies follow an atom economic path. Thus, chemists are constantly posed with challenges during the synthesis of complex molecules, particularly all carbon quaternary centers. Spirocyclic structures are found in wide range of natural compounds isolated from various natural resources. The complexity of these ring structures is represented by the quaternary carbon center and two fused rings or spirocyclane, first coined by Baeyer in the early 1900s.[7] The inherent steric factors observed in these systems enhance the difficulty level during their syntheses.

Stereoselective methodologies in constructing spirocenters have led to the total syntheses of several spirocenter containing natural products over the last decade.[4,7,8] Approaches to spirocycle formation such as intramolecular contraction, Diels–Alder reactions, transition metal mediated reactions prior to 2010, among others will not be described as they have been previously reviewed.[3–6] New methodologies have been successfully applied to the synthesis of spirocyclic systems, containing medium to large size rings with controlled stereochemistry, allowing for the synthesis of diverse compound libraries of medicinal interest.[8] Enantioselectivity and diastereoselectivity control has been mostly promoted by ligand controlled transformations and this area of research continues to expand.[9]

As the field of medicinal chemistry directs its attention towards the intriguing biological properties of spirocycles, the synthesis of such complex structures will persist as an active area of research, catalyzing the development of new methodologies.[8]

The content of this report is organized into two general categories, recent advancements in chemical reactions to generate all-carbon non-spiro quaternary stereocenter, and all carbon spiro-quaternary centers. The rational for the presented grouping of reactions is based on the nature of the newly formed all-carbon quaternary stereogenic center. Section A, methods to non-spiro all-carbon quaternary centers, includes chemical transformations that generate the type of bonds in either acyclic or monocyclic system (Fig. 2). Section B, methods to spiro all-carbon quaternary centers, includes methods involving the generation of bicyclic systems (Fig. 2). The sections were also grouped according to reaction mechanisms, featuring similar chemical reactivity such as the intermolecular new bond formation promoted by an external agent (metal catalyzed reactions as show in section A), while most examples in section B involved the intramolecular formation of the key bond or the intermolecular formation of two new bonds (red color indicates the newly generated bonds, Fig. 2).

3. Section A: methods to non-spiro all-carbon quaternary centers

3.1. Metal-mediated reactions: titanium

A practical synthesis to the construction of a broad range of acyclic quaternary carbon centers mediated by Titanium was disclosed by Tsubouchi and co-workers.[10c] A highly diastereoselective reaction of γ,γ-disubstituted allyl-titanium species **3**—generated in situ from allyl sulfides **1** and reagent **2**, with aliphatic or aromatic ketones **4** to provide the corresponding highly functionalized acyclic products **5** or **6** (Scheme 1). The resultant product bearing two adjacent fully substituted carbon stereocenters with excellent diastereoselectivity (*dr* up to 99:1) was obtained in good yields. The reaction proceeds using titanocene (II) 1-butene complex (CP_2Ti) in a mixture of cyclopentylmethyl ether (CPME) and tetrahydrofuran (THF) at low temperature for optimal results. This method can generate large compound libraries from the stereochemically defined γ,γ-disubstituted allyl sulfides **1**, which are readily prepared from the corresponding alcohol substrates. Furthermore, the method is complementary to previously disclosed diastereoselective allylation of ketones with γ-monosubstituted allyl metalloid/metal (B, Si, In, V, and others).[10a,b]

Thermodynamically stable allyltitanocenes bearing an *E* conformation are preferentially generated from both stereoisomers of γ-monosubstituted allyl sulfides. In the case of γ,γ-disubstituted allyl sulfides, the results indicate that the desulfurizative titanation of the highly substituted allyl sulfides proceeds with retention of configuration. A few exceptions, such as cinnamyl sulfide (Z), resulted in the *E* configuration of allyl titanocene, but in most examples, the resulting allyl titanocene intermediate **3** is conformationally stable to react with ketone substrate **4** via a chair-like, six-membered transition state with the bulky substituent of the ketone occupying the pseudoequatorial position. Therefore, the ketone plays a critical role in the stereospecific and diastereomeric control of the resultant homoallyl alcohol, regardless of the geometry of the allylic sulfide **1**. For instance, the reaction of butan-2-one is less diastereoselective than that of 1-cychohyxylethan-1-one, with resultant diastereomeric ratios of 3:17 and 99:1, respectively.

3.2. Metal-mediated reactions: iron, magnesium, and silver complexes

Carbon-economic reactions refer to those chemical transformations whereby all the atoms in the starting materials remain part of the desired product and the reaction mediating reagents are used in catalytic amounts. Such an example is the asymmetric

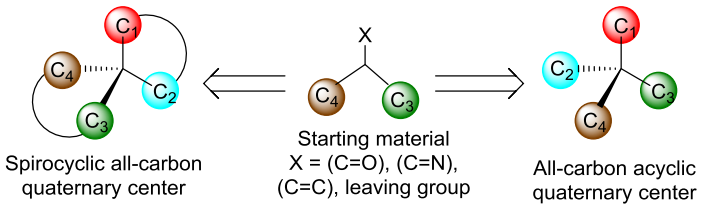

Fig. 1. All carbon-quaternary centers.