Tetrahedron Letters 49 (2008) 4220–4222

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Catalytic multicomponent cycloaddition assembling three different substances to form highly substituted bicyclo[4.2.0]octanes

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ARTICLE INFO

Article history:
Received 5 April 2008
Revised 30 April 2008
Accepted 2 May 2008
Available online 6 May 2008

ABSTRACT

A catalytic multicomponent (4+2)–(2+2) cascade cycloaddition process assembling three different substances has been developed. The process is able to rapidly provide a highly substituted bicyclo[4.2.0]octane skeleton from a 2-siloxydiene and two molecules of α,β-unsaturated carbonyl partners. The MCR process is accompanied by stereoselective formation of four carbon–carbon bonds and four stereogenic centers in a single operation.

A variety of natural and non-natural substances that contain polycyclic rings and an assortment of stereogenic centers have been found to exhibit attractive and specific biological activities. Owing to this, synthetic organic chemists are constantly confronted with the task of developing new reactions that can be used to prepare these complex targets in concise fashions starting from simple and readily available materials. An innovative strategy developed for this purpose relies on the use of highly convergent multicomponent reactions (MCRs).[1–3] Major advantages of MCRs, in which multiple covalent bonds are formed in a single step, include time- and cost-saving, atom economy, environmental benignancy, and applicability to diversity-oriented synthesis and combinatorial chemistry. In spite of the intense interest in MCRs, only a limited effort has been given to applications of these processes to the synthesis of stereochemically complex polycyclic targets.[3]

Cycloaddition reactions efficiently generate cyclic compounds from simple starting materials. Consequently, MCRs that incorporate multiple cycloaddition reactions should serve as the foundation for novel approaches to the stereocontrolled preparation of complex polycyclic substances. Recognizing that polycyclic cyclobutanes are common ring systems found in a variety of natural products (Fig. 1),[4–8] we focused on MCRs that incorporate the new catalytic (2+2) cycloaddition reaction. Recently, we described that $EtAlCl_2$ promoted (4+2)–(2+2) cascade cycloaddition of a 2-siloxybutadiene with 2 equiv of an α,β-unsaturated ester. The reaction involves Diels–Alder reaction between a 2-siloxydiene and an α,β-unsaturated ester followed by (2+2) cycloaddition between the formed silyl enol ether and the second α,β-unsaturated ester to yield a highly functionalized bicyclo[4.2.0]octane.[9] The MCR process can generate four carbon–carbon bonds, two rings, and up to eight stereogenic centers in a single operation. With the successful results, our attention has been directed toward a multicomponent cycloaddition that assembles three different substances into a bicyclo[4.2.0]octane skeleton at once. In order to achieve the challenging task, control of the rates of two different types of cycloaddition processes is crucial. In this Letter, we report the results of our efforts to develop a catalytic (4+2)–(2+2) cycloaddition assembling three different components to produce highly substituted polycyclic skeletons.

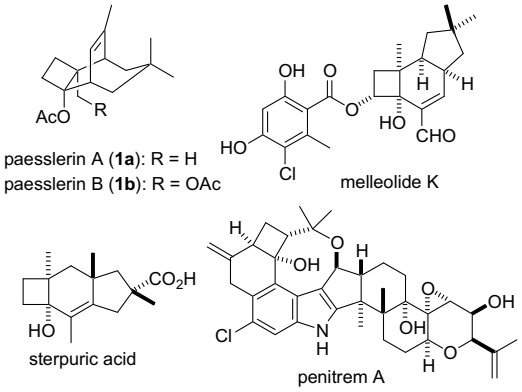

Figure 1. Naturally occurring substances having cyclobutane skeleton.

In our previous study toward the synthesis of the proposed structure of paesslerin A (**1**),[4] stereoselective construction of tricyclo[4.3.2.0^{2,5}]undecadiene **2** has been accomplished in the reaction of 2-siloxydiene **3** and bimolecular amount of propiolate **4** promoted by $EtAlCl_2$. Then, regioselective 1,4-reduction of **2**, followed by several appropriate transformation, lead to completion

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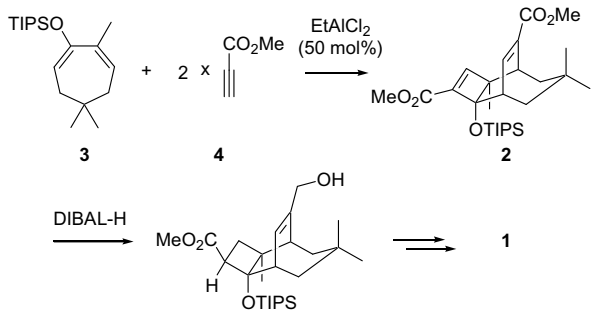
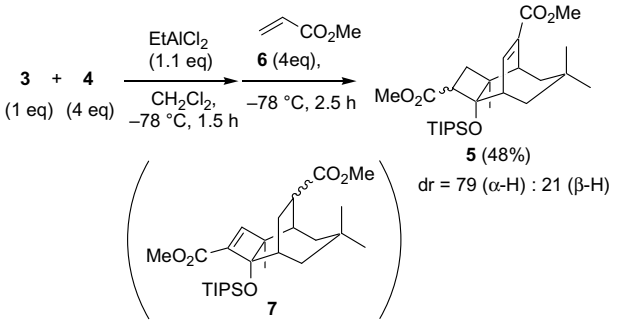
doi:10.1016/j.tetlet.2008.05.001



Scheme 1. $EtAlCl_2$-catalyzed (4+2)–(2+2) cycloaddition of 2-siloxydiene **3** with 2 equiv of propiolate **4**, and synthesis of a proposed structure of paesslerin A (**1**).

of synthesis of **1** (Scheme 1). We envisaged that assembly of three different substances such as a 2-siloxydiene, a propiolate and an acrylate by (4+2)–(2+2) cascade cycloaddition would produce tricyclo[4.3.2.$0^{2,5}$]undecene **5**, which would be an advanced synthetic intermediate of **1**. Reaction of a mixture of 2-siloxydiene **3** (1 equiv), propiolate **4** (2 equiv), and acrylate **6** (2 equiv) promoted by $EtAlCl_2$ (1 equiv) was explored first. Unfortunately, a complex product mixture was formed and neither of the adducts **5** nor **7** could be isolated by using silica gel chromatography. Based on our knowledge that (2+2) cycloaddition of a silyl enol ether with a propiolate does not proceed at −78 °C,[9,10] an alternative protocol involving stepwise addition of the unsaturated ester substrates was attempted. $EtAlCl_2$ was added dropwise to a solution of **3** and **4** (2 equiv) at −78 °C. After completion of (4+2) cycloaddition step (monitored by TLC) **6** (2 equiv) was added to result in formation of **5** (less than 15% yield). Optimization of this procedure showed that **5** could be obtained in 48% yield as a 4:1 diastereomeric mixture (determined by ^1H NMR) along with a trace amount of **2** when 1.1 equiv of $EtAlCl_2$ are used and the reaction is run at −78 °C (Scheme 2). In contrast, when this sequential process is conducted at 0 °C, formation of tricyclic ester **2** mainly takes place. 2D NMR analysis of major diastereomer of **5** has revealed that the adduct **5** has the same relative stereochemistry. The stereochemical outcome would be explained as shown in Figure 2. At the (2+2) cycloaddition stage, acrylate **6** approaches from less hindered site of the silyl enol ether intermediate, which was produced by Diels–Alder reaction of 2-siloxydiene **3** and propiolate **4**. The stereochemistry of ester substituent would be determined at the final C–C bond formation (aldol-type addition) of the zwitter ionic intermediate by the steric repulsion against the bulky siloxy substituent.[11]

Discrimination between the reactivity of two α,β-unsaturated carbonyl substrates in the initial Diels–Alder reaction is essential for the success of three-component MCR processes. In this respect,



Scheme 2. (4+2)–(2+2) Multicomponent cycloaddition of 2-siloxydiene with propiolate and acrylate (three different components).

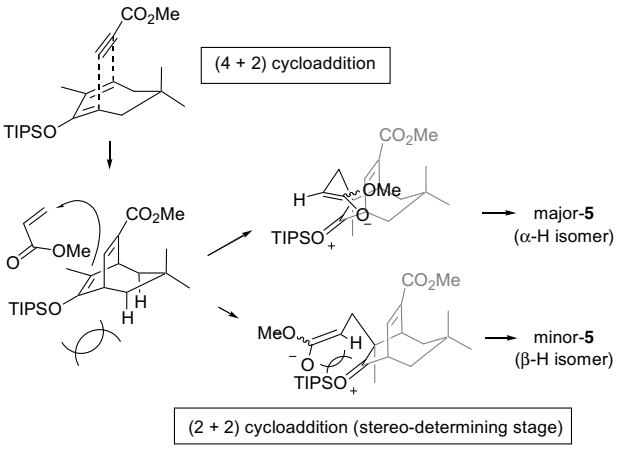
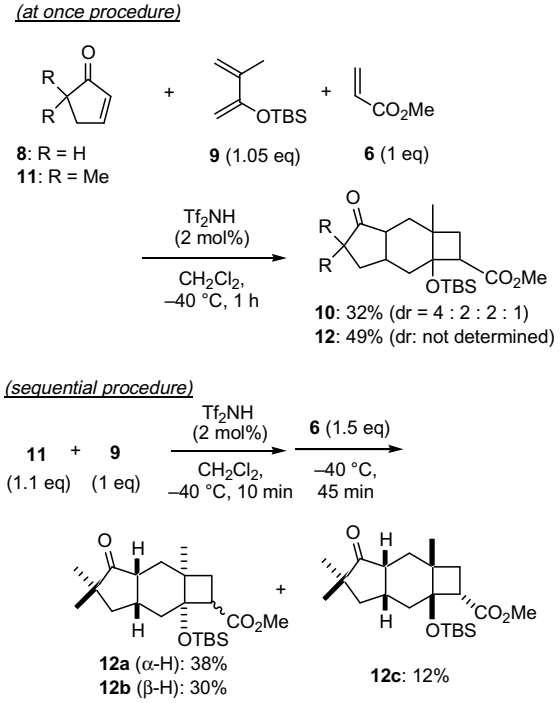


Figure 2. Plausible mechanism for the stereoselectivity at the (2+2) cycloaddition stage.

we envisioned that more dienophilic unsaturated ketones would undergo Diels–Alder reactions in preference to acrylate esters. However, no desired MCR product was obtained under any conditions using $EtAlCl_2$ as a catalyst. Quite recently, we have reported that trifluoromethanesulfonylimide (triflic imide; Tf_2NH)[12] serves as a highly active catalyst for (2+2) cycloadditions of silyl enol ethers with acrylates.[10] It has been revealed, that in the reaction, Tf_2NH acts as a pre-catalyst to produce a strong Lewis acidic catalyst, R_3SiNTf_2, through reaction with silyl enol ethers. Stimulated by the discovery, we evaluated the organo-acid catalyst for MCR process. In accord with this, we observed that addition of 2 mol % of Tf_2NH to a near equimolar mixture of 2-cyclopentenone (**8**), siloxydiene **9**, and acrylate **6** in CH_2Cl_2 at −40 °C led to formation of the desired tricyclo[6.3.0.$0^{3,6}$]undecane **10** in 32% yield as a 4:2:2:1 mixture of four diastereomers (Scheme 3). The ratio of the stereo-



Scheme 3. Tf_2NH-catalyzed (4+2)–(2+2) multicomponent cycloaddition of a siloxydiene with an enone and an acrylate by at once procedure (above) and sequential procedure (bottom).

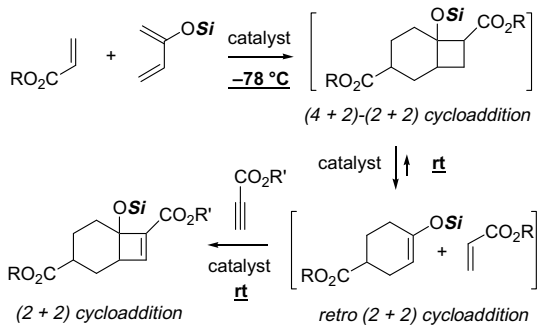
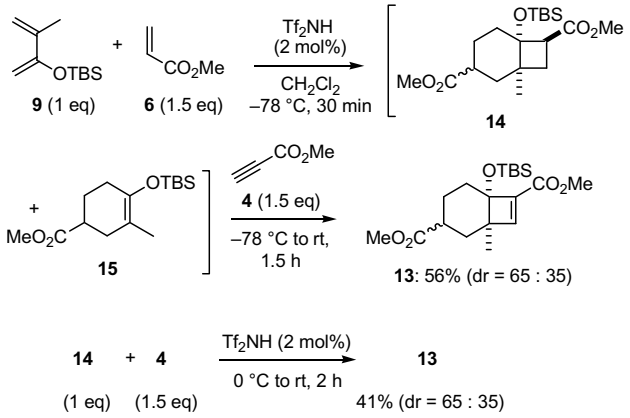


Figure 3. A concept for an alternative (4+2)–(2+2) multicomponent cycloaddition utilizing thermodynamic equilibrium.



Scheme 4. Tf_2NH-catalyzed (4+2)–(2+2) multicomponent cycloaddition utilizing a retro (2+2) cycloaddition process.

isomers was determined by ^1H NMR. Reaction of the dimethylenone analog **11**[13] under the same conditions yields **12** in 49% yield as a mixture of four diastereomers (ratio undetermined). These observations show that although chemoselective discrimination of the substrates participating in this MCR is possible, issues related to chemical yield and the diastereoselectivity need to be addressed. Further optimization of the process made it clear that the sequential addition procedure results in more efficient MCR, as demonstrated by the formation of tricyclic products **12a**,**12b**, and**12c** in 38%, 30%, and 12% yields, respectively (isolated yields). NOESY experiments have revealed that the former products **12a** and **12b** possess the same relative configurations as found in skeleton of natural sesquiterpenoids, sterpranes (see Fig. 1).[6]

During the course of our earlier studies of catalytic (2+2) cycloadditions of silyl enol ethers and acrylates giving 2-siloxycyclobutyrylcarboxylates, we observed that retro-reactions proceeded in the presence of the catalysts, such as $EtAlCl_2$ and Tf_2NH, at ambient temperature.[14,15] On the other hand, no (or almost no) retro-process is detected at ambient temperature for 2-siloxycyclobutenylcarboxylates, that are formed from silyl enol ethers and propiolates. These properties serve as the foundation of an alternative strategy for the design of efficient three component MCR process. Thus, we anticipated that bicyclo[4.2.0]octanes, generated at −78 °C from siloxydienes and 2 equiv of acrylate esters at −78 °C, would undergo the retro (2+2) process at elevated temperature followed by addition of a propiolate to furnish the desired bicyclo[4.2.0]octenes (Fig. 3). As predicted, reaction of siloxydiene **9** with methyl acrylate (**6**) in the presence of Tf_2NH at −78 °C, followed by addition of methyl propiolate (**4**) at the same temperature and warming to ambient temperature, leads to formation of bicyclo[4.2.0]octene **13** in 56% yield (Scheme 4). Production of the intermediate adducts **14** and **15** can be monitored by TLC but neither **15** nor a bicyclo[4.2.0]octadiene, which would be formed from **9** and 2 equiv of propiolate **4**, is detected by this method when the temperature of the reaction mixture is raised to ambient temperature. Moreover, the mechanism for the process, involving a retro (2+2) cycloaddition, was evidenced by the observation that reaction of **14** with methyl propiolate (**4**) in the presence of Tf_2NH (0 °C to ambient temperature) yields bicyclo[4.2.0]octene **13** in 41% yield.

In summary, we have developed a novel multicomponent (4+2)–(2+2) cascade cycloadditions, which allows for the rapid construction of polysubstituted bicyclo[4.2.0]octanes starting from three different simple components. It is noteworthy that the MCR process is accompanied by stereoselective formation of four carbon–carbon bonds and four stereogenic centers in a single operation. In addition, we have discovered that triflic imide (Tf_2NH) is a highly efficient catalyst for the cascade process.

Acknowledgments

The work was supported by a Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science, and Technology, Japan, and the Uehara memorial foundation.

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