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Chemoselective reactions: Toward the synthesis of biologically active natural products with anticancer activities*

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Abstract: Leucascandrolide A and migrastatin were synthesized efficiently by using chemoselective reactions such as olefin metatheses. The use of an iron-catalyzed cross-coupling reaction overcame difficulties encountered with palladium-catalyzed processes in our synthetic approach toward spirangien A.

Keywords: natural products; total synthesis; crotyltitanation; allyltitanation; cross-metathesis; ring-closing metathesis; chemoselective reactions; cross-coupling; iron.

INTRODUCTION

Cancer represents one of the most severe health problems. In 2005, 7.6 million of the 58 million deaths in the world were attributed to cancer, and in 2030, the annual number of deaths from cancer should increase to 11.4 million [1]. Substantial progresses in our ability to treat this deadly disease will critically depend on the discovery of new anticancer drugs and the development of more effective clinical strategies. However, in spite of impressive advances in the development of signal-transduction kinase inhibitors for cancer, receptor, or ligand-directed antibodies, the search for improved or new anticancer agents still constitutes an important part of modern drug discovery. By examining anticancer drugs from the last 66 years, of the 155 available small molecules, 113 (73 %) are nonsynthetic, with 47 % actually being either natural products or natural product-derived molecules [2]. Indeed, natural products are often a great source of inspiration for new structures and/or activities.

As natural products are in most cases isolated in small quantities, it is necessary to synthesize them in order to develop biological tests and new synthetic strategies giving access to analogs. The latter can be used to lead structure–activity relationship (SAR) studies and may even reveal more activity than the natural product itself. To do so, the synthetic methods employed have to be versatile, efficient, and chemoselective in order to avoid protection–deprotection steps which are material- and time-consuming. Furthermore, shortcuts such as one-pot reactions can be used and may reveal more efficiency than the corresponding step-by-step process.

For our part, we were particularly interested in the synthesis of leucascandrolide A, migrastatin, and spirangien A, all of these compounds were isolated from natural sources and exhibit promising anticancer activities.

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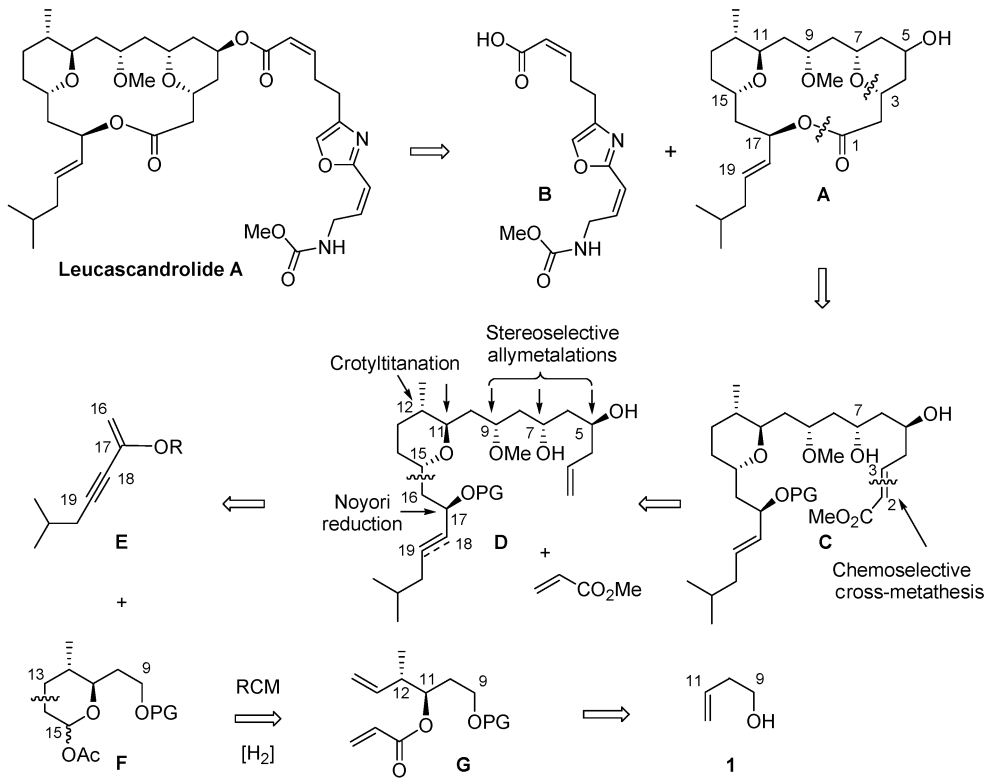
LEUCASCANDROLIDE A

Leucascandrolide A is a structurally unique macrolide isolated in 1996 from the sponge *Leucascandra caveolata*, extracted from the northeastern coast of New Caledonia in the Coral Sea [3]. This compound has shown anticancer activities against human KB and P388 tumor cell lines displaying IC_{50} of 0.05 and 0.26 μg/mL, respectively. Recent reports indicate that leucascandrolide A is no longer available from its original natural source due to the fact that this compound would not be a metabolite of *Leucascandra caveolata* but the one of an opportunistic bacteria [4]. Because of its structural complexity and its interesting biological properties, leucascandrolide A has solicited considerable interest among organic chemists [5–7]. In most cases, the synthesis of leucascandrolide A was achieved by coupling the macrocyclic hydroxylactone **A** with the oxazole containing carboxylic acid **B** either by esterification or by using a Mitsunobu reaction.

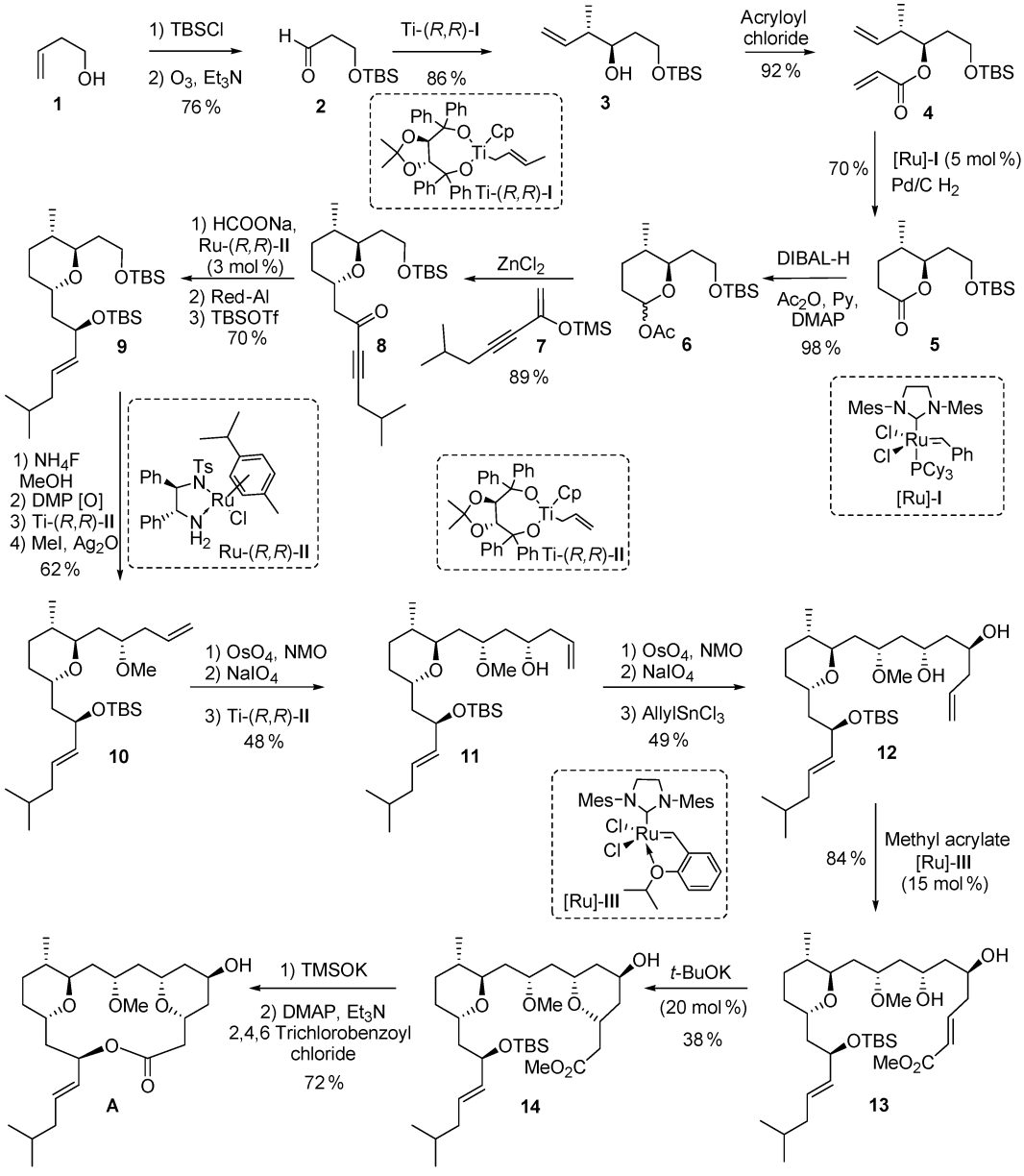
One of the challenges in this synthesis is the control of the stereogenic centers present in macrolactone **A** by using the minimum of protecting groups in order to shorten the synthesis. This should be feasible by using very chemoselective reactions such as cross-metathesis (CM), ring-closing metathesis (RCM), and enantioselective allyltitanations [8]. The unsaturated hydroxy ester **C** would be the precursor of **A**, as the *cis*-tetrahydropyran present in this latter compound would be obtained by using an intramolecular 1,4-addition of the hydroxy group present at C7 on the unsaturated ester. Ester **C** would be synthesized by using an olefin CM between methyl acrylate and the highly functionalized olefin **D**. In compound **D**, the stereogenic centers at C5, C7, C9, C11, and C12 would be controlled by using highly stereoselective allylmetalations of aldehydes and the C17 stereogenic center would be controlled by performing a ruthenium-catalyzed Noyori reduction of a propargylic ketone [9]. The addition of an



Scheme 1

enol ether of type **E** to an oxonium species derived from **F** would allow the formation of the *trans*-tetrahydropyran moiety present in leucascandrolide A. To obtain the acetyl lactol **F**, an RCM would be applied to diene **G**, which would in turn derive from but-3-en-1-ol (**1**) (Scheme 1).

The synthesis of fragment C9–C15 starts with the transformation of but-3-en-1-ol (**1**) to aldehyde **2** in two steps. The addition of the highly face-selective titanium complex Ti-(*R*,*R*)-**I** [8] to aldehyde **2** allowed the control of the stereogenic centers at C11 and C12, producing the desired homoallylic alcohol **3** (86 % yield). This alcohol was transformed into the unsaturated ester **4**, and two one-pot sequences were successfully applied to **4**, thus leading to the desired acylated lactol **6**. The first one-pot reaction involved a tandem RCM/hydrogenation to form the unsaturated lactone **5**, and the second one-pot reaction was the transformation of the lactone to compound **6** by using a diisobutylaluminum hydride (DIBAL-H) reduction followed by an acetylation [10]. An oxonium intermediate was generated from **6** ($ZnCl_2$) and trapped with the silyl enol ether **7** to afford *trans*-tetrahydropyran **8** (*trans/cis* = 13/1, 89 % yield). After reduction of the ketone by using Noyori catalyst Ru-(*R*,*R*)-**II** under phase-transfer conditions (HCO_2Na, *n*-Bu_4NCl, H_2O/CH_2Cl_2), the desired propargylic alcohol was formed and reduced with Red-Al to produce compound **9** after protection of the obtained allylic alcohol (TBSOTf). After chemoselective deprotection of the primary alcohol (NH_4F, MeOH), oxidation to the corresponding aldehyde by Dess–Martin periodinane (DMP), treatment with the highly face-selective titanium complex **Ti-**(*R*,*R*)-**II**, and etherification (Ag_2O, MeI), compound **10** was isolated in 62 % yield. Due to the presence of the bulky *t*-butyldimethylsilyl protecting group at C17, the internal double bond at C18-C19 was sterically hindered and protected against oxidative conditions. Indeed, compound **10** was transformed to allylic alcohol **11** by using a chemoselective oxidative cleavage ($OsO_4/NaIO_4$) and an enantioselective allyltitanation [Ti-(*R*,*R*)-**II**] to control the stereogenic center at C7. An iterative process of the above-mentioned chemoselective oxidative cleavage ($OsO_4/NaIO_4$), followed by a diastereoselective allylstannylation of the obtained β-hydroxyaldehyde ($allylSnCl_3$, –78 °C) afforded the *syn*-1,3-diol **12** [11]. Two steps were then necessary to build up the *cis*-tetrahydropyran ring using a CM between **12** and methyl acrylate followed by the treatment of the obtained hydroxy unsaturated ester **13** under basic conditions (*t*-BuOK, THF, 0 °C) [12] to produce **14** in two steps by applying reported procedures [5d,6e]. The macrocyclic lactone of leucascandrolide A was synthesized in 25 steps from but-3-en-1-ol (**1**) by using only two protective groups thanks to the use of chemoselective reactions (Scheme 2) [13]. This synthesis of macrolactone **A** appears to be one of the shortest by considering the total number of steps.

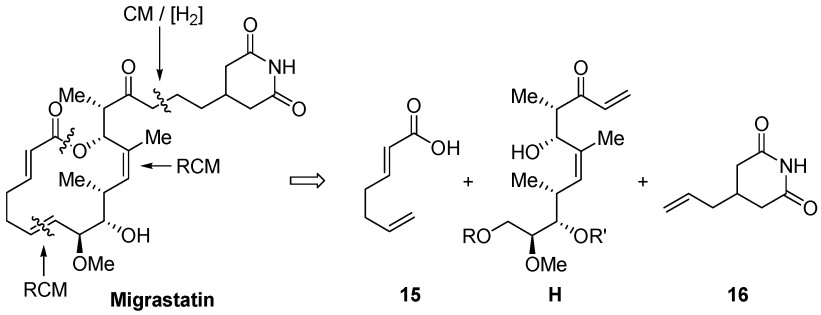


Scheme 2

MIGRASTATIN

Migrastatin is a naturally occurring macrolide isolated from broth cultures of two strains of *Streptomyces* [14]. This compound has been shown to inhibit cell migration in a wide range of tumor cell lines at micromolar concentrations. Due to its unusual mode of action and its potential use in anticancer treatment, we were attracted to this compound and a convergent and flexible synthesis was designed in order to furnish the natural product itself but also to give access to analogs. The key steps in our synthesis were based on the use of three metathesis reactions, one RCM to control the (*Z*)-double bond at C11–C12, one to build up the (*E*)-double bond at C6–C7, and a CM reaction to install the alkyl

glutarimide side-chain thus creating the C16–C17 bond. The stereogenic centers at C9, C10 and C13, C14 would be controlled by using two enantio- and diastereoselective crotylmetalations of aldehydes. The use of these reactions implies the synthesis of fragments **H**, **15** and **16** (Scheme 3).

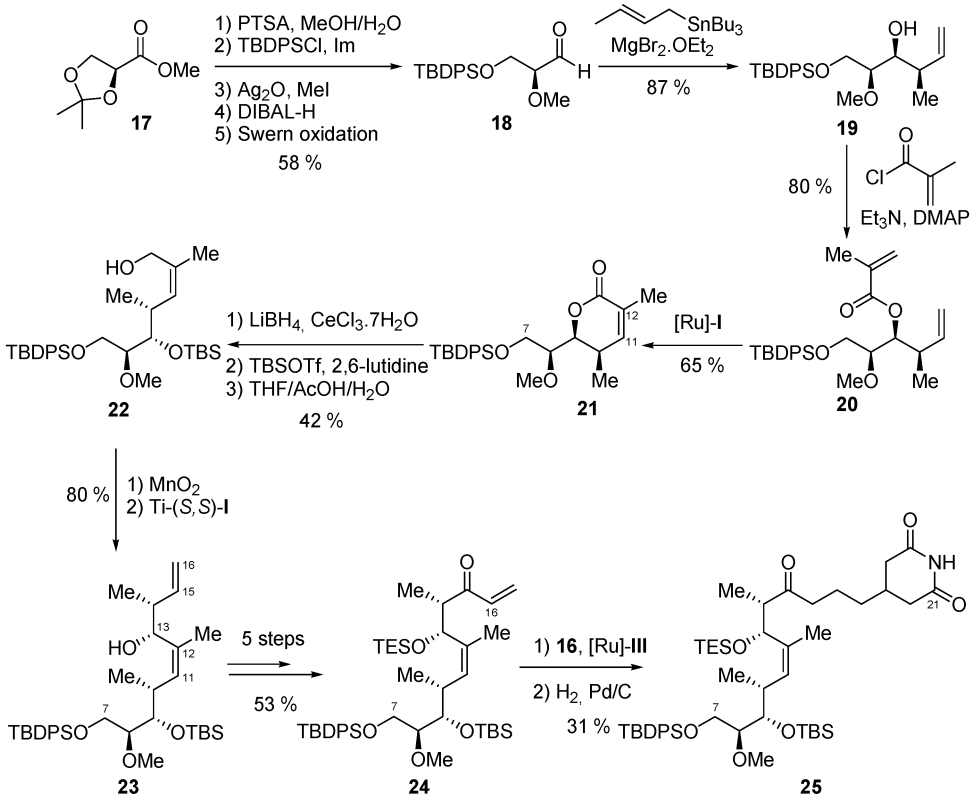


Scheme 3

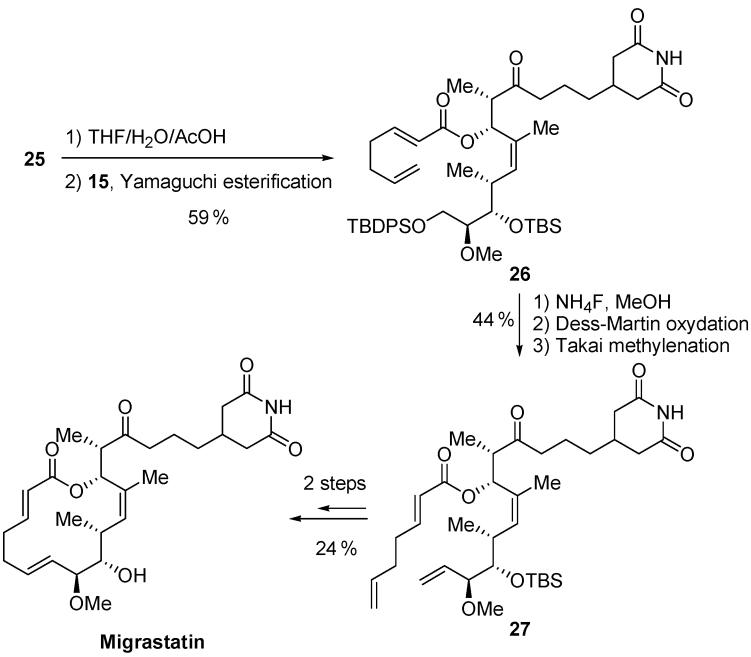
Compound **16** was synthesized in five steps from allyldiethylmalonate, and the unsaturated carboxylic acid **15** was prepared from pent-4-enal [15]. Most challenging was the synthesis of compound **H**, incorporating the five stereogenic centers of migrastatin.

Our synthesis of fragment **H** started from methyl ester **17**, which was transformed to the unstable aldehyde **18**. The latter was directly treated with but-2-enyl[tri(*n*-butyl)]stannane in the presence of $MgBr_2 \cdot OEt_2$ to yield *syn*,*syn*-stereotriad **19** with good diastereoselectivity (dr = 90/10, yield = 87 %) [16]. As up to now, no CM catalyst is available to induce a (*Z*)-double bond, an RCM was used to control the (*Z*)-stereochemistry of the C11–C12 trisubstituted double bond in **21**. Compound **21** was transformed to the (*Z*)-allylic alcohol **22** by reduction of the lactone obtained after having applied an RCM to the dienic ester **20**. In order to control the last two stereogenic centers at C13 and C14, alcohol **22** was oxidized to an aldehyde which was directly treated with the highly face-selective crotyltitanation complex Ti-(*S*,*S*)-**I** leading to **23**. This latter compound was transformed in five steps to the vinylketone **24**. We have to point out that the triethylsilyl protecting group at C13 is of great importance as we anticipated the protection of the C11–C12 double bond from the next CM and hydrogenation that have to be used to complete the synthesis of migrastatin. Enone **24** was first coupled with allylglutarimide **16** by using a chemoselective CM reaction, and the resulting cross-product was selectively hydrogenated to produce **25** (Scheme 4).

After selective deprotection of the hydroxy group at C13, a Yamaguchi esterification was achieved with a mixed anhydride prepared from the carboxylic acid **15** to afford compound **26**, which was transformed in three steps to the polyenic ester **27**. As previously described [17], compound **27** was cyclized by using an RCM as the key step, and deprotected to produce migrastatin [18] (Scheme 5).



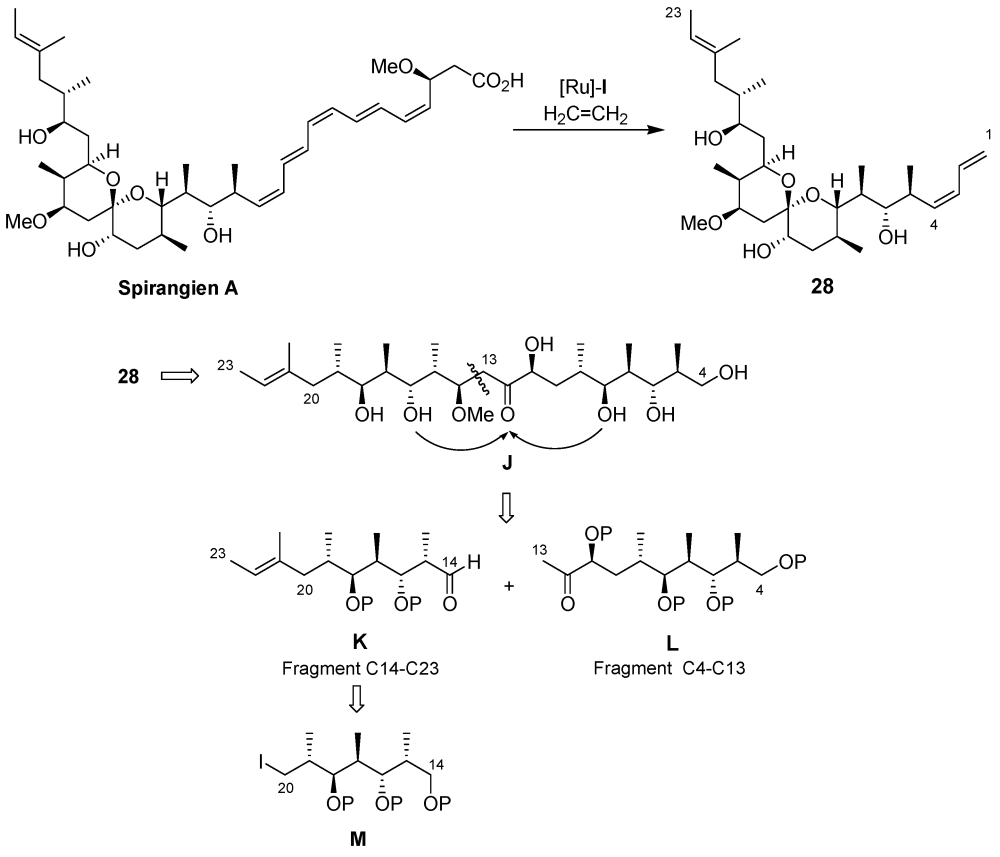
Scheme 4



Scheme 5

SPIRANGIEN A

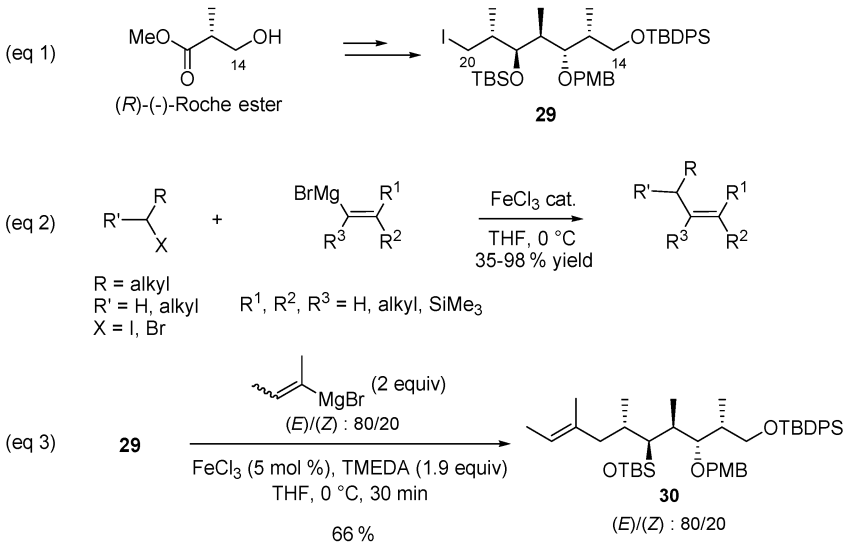
Spirangien A was isolated from the epothilone-producing myxobacterium *Sorangium cellulosum* and has shown a cytotoxic activity (IC_{50} = 0.7 ng/mL against L929 mouse fibroblast cell line) [19]. Interestingly, the 1,3-diene **28**, obtained after treatment of spirangien A with Grubbs' catalyst second-generation [Ru]-**I** under ethylene, retained one-tenth of the cytotoxic activity of spirangien A (IC_{50} = 7 ng/mL against L929). Due to the simplification of the structure of **28** compared to spirangien A, we embarked on the synthesis of this compound. 1,3-Diene **28** would be obtained by spiroketalization of compound **J**, which would be formed by an aldol condensation of aldehyde **K** with ketone **L**. At first, we were interested in the synthesis of aldehyde **K**, which would be obtained by using a cross-coupling reaction between a vinyl metal and an alkyl iodide of type **M** (Scheme 6).



Scheme 6

The alkyliodide **29** was successfully prepared from the (*R*)-Roche ester (Scheme 7, eq. 1) but its palladium-catalyzed cross-coupling with a vinyl metal or a vinyl halide failed. We next turned our attention to the potential of iron-catalyzed cross-coupling based on the previous works by Cahiez et al. [20] and Nakamura et al. [21], we were able to develop a cross-coupling reaction between alkyl halides and alkenyl Grignard reagents catalyzed by iron salts [$FeCl_3$ (10 mol %), TMEDA (1.9 equiv)] (Scheme 7, eq. 2) [22].

By applying these conditions to alkyl iodide **29** and 2-butenylmagnesium bromide, we were able to produce successfully **30**, the C14–C23 fragment of spiroketal **28** with a yield of 66 % (Scheme 7,



Scheme 7

eq. 3). Having completed the synthesis of a precursor of the fragment of type **K**, the synthesis of fragment **L** is on its way.

Due to the use of very chemoselective methodologies, leucascandrolide A and migrastatin were obtained efficiently. In the case of spirangien A, the failure in using usual coupling reactions has forced us to build up a very efficient and powerful methodology that should allow us to complete the synthesis of this product.

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