Chapter 17
Synthesis of Biologically Active Nitrogen and Sulfur-Containing Terpenoids

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ABSTRACT

New, original, and ecologically pure methods for the synthesis of compounds with hybrid terpene and heteroatomic functional groups or fragments have been developed, starting from accessible (+)-sclareolide, obtained from (-)-sclareol, well-known labdane diterpenoid diol extracted from the waste of Clary sage (Salvia sclarea L.) remaining after extracting the essential oil. The natural origin of terpene compounds supposes biocompatibility, selective biological activity, and low toxicity. The compounds with combined skeleton were obtained by coupling some terpene derivatives (acids, chloroanhydrides, bromides) with azaheterocyclic compounds or heterocyclization of some intermediates such as hydrazides, hydrazincarbothioamides, or thiosemicarbazones. A series of over 120 newly obtained substances were subjected to biological testing, of which 10 showed pronounced antifungal and antibacterial activity, two amides showed pronounced antioxidant activity, and two derivatives with guanidine fragments showed high antitumor activity.

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INTRODUCTION

Microbial infections have spread rapidly in recent years, becoming one of the most important concerns in countries around the world (Grahman, 2001; Greenwood et al., 2007). These global trends stimulate the design of new molecular structures with antimicrobial properties, which could lead to new and effective medicinal preparations for their treatment. One of the most important and accessible sources of new biological compounds is natural products due to their origin implies biocompatibility, selective biological activity, and low toxicity. These include terpenoids, a group of compounds of natural and, as well, of synthetic origin, which are widely used in medicine, pharmaceuticals, cosmetics, and agriculture (Fraga, 2013; Jansen & De Groot, 2004). Particular attention is paid to terpenic compounds that possess multiple biological activities, such as anticancer (Allouche et al., 2009), antioxidant, antimicrobial (Komala et al., 2010), antifungal (Zhou et al., 2011), antimalarial (Lhinhatrakool et al., 2011), antidiabetic (Zhao et al., 2012).

Several studies to date confirm that the presence of heteroatoms, especially nitrogen or sulfur, often increases the biological activity of terpenic compounds. Other teams of authors have reported an even greater increase in the activity of terpenes in cases when their molecules contain some heteroatomic functional groups or fragments, or heterocyclic units.

Recently, the synthesis of molecules with a hybrid skeleton has emerged as a powerful tool in the design of drugs and especially preparations with promising biological activity (Viegas-Junior et al., 2007). This approach is based on the combination of several pharmacophores, which produce compounds with a combined molecular structure and have a higher bioactivity than some known drugs.

Our research was focused on the development of original methods for the preparation of new functionalized bicyclic nitrogen and sulfur-containing derivatives based on the available natural diterpenoid - sclareol and the designing of natural chiral molecules of interest for the pharmaceutical industry.

The functionalization of bicyclic sclareol's derivatives, including sesquiterpenoids have been performed both in the side chain and in the C_7 position of cycle B, have led to lactams and other products containing amino groups, or azine, hydrazide, hydrazide and guanidine fragments, as well as heterocyclic units.

BACKGROUND

Synthesis of Norlabdane Compounds With Amino Group

Many drimane sesquiterpenoids, including their prototype drimenol 1, exhibit various biological activities (Kuchkova et al., 2009). Therefore, it seemed interesting to synthesize 11-aminodrim-7-ene 2, an analog of drimenol with an amino group, in order to study its biological activity.

11-Aminodrim-7-ene 2 was synthesized from drimenol in four steps. First, drimenol 1 was oxidized into drimenal 3, and then its oxime 4 was dehydrated by *p*-tosylchloride or acetic anhydride in pyridine to form 9-cyano-11-nordrim-7-ene 5, followed by its reduction with $LiAlH_4$ in the presence of anhydrous $AlCl_3$ produced 11-aminodrim-7-ene. The reaction of 9-cyano-11-nordrim-7-ene 5 with $NaBH_4$, and $CoCl_2 \cdot 6H_2O$ produced a mixture of drimenylamine 2 and 7,8-dihydrodrimenylamine 6 in a 2:1 ratio (Figure 1), that is interesting as compounds with potential biological activity.

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