



Digest paper

An overview of the total synthesis of africane-type sesquiterpenoids

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ABSTRACT

Africane-type sesquiterpenoids consist of a bicyclo[5.3.0]decane structure and have been isolated from various natural environments. Their characteristic C–C bond motifs, including a seven-membered ring core, fascinate many synthetic organic chemists. Thirteen total syntheses have been reported over the past four decades. The purpose of this digest is to provide an overview of these total syntheses of africane-type sesquiterpenoids, with an emphasis on methods for constructing the seven-membered ring structure.

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Introduction

Africanene-type sesquiterpenoids possess a 5-7-3 tricyclic structure. The first africanene natural product to be isolated was africanol (**1**), isolated from the soft coral *Lemnalia africana* in 1974 by the Braekman group.¹ Subsequently, many natural sesquiterpenoids structurally similar to africanol have been discovered and therefore were named 'africanes'.²

Africanes are widespread in various natural environments. For example, $\Delta^{9(15)}$ -africanene (**2**) is a natural product isolated from many terrestrial sources and marine species, such as soft coral,^{3a,3b} liverwort,^{3c} and angiosperm plants.^{3d,3e} This interesting observation can be rationalized by the proposed biosynthetic pathway^{1,4} from a very common sesquiterpenoid, humulene (**3**), to africanes (Scheme 1). Transannular cyclization of **3** simultaneously forms the africanene skeleton and the highly reactive carbocation intermediates **4**, which induces various reactions to lead to a number of africanes, including *trans*-fused ring compounds (e.g., **2**), *cis*-fused ring compounds (e.g., **6**⁵ through africanene (**5**)¹) and hydroxylated compounds (e.g., **1**).

In general, molecular diversity can provide an enormous opportunity for synthetic chemists to establish new strategies applicable to the synthesis of various structurally complex natural products. From this perspective, africanes of adequate molecular size for demonstrating the new strategies fascinate synthetic organic chemists as a means of demonstrating their new strategies: e.g., the control of *cis/trans* selective cyclization, the assembly of three carbon rings without stereochemical scrambling, etc.

In addition to the interest in the fused-ring system of africanes, their medium-sized ring core is an appealing synthetic target.⁶ The medium-sized ring (seven to ten membered carbocycles) system is generally difficult to be constructed due to unfavorable enthalpic

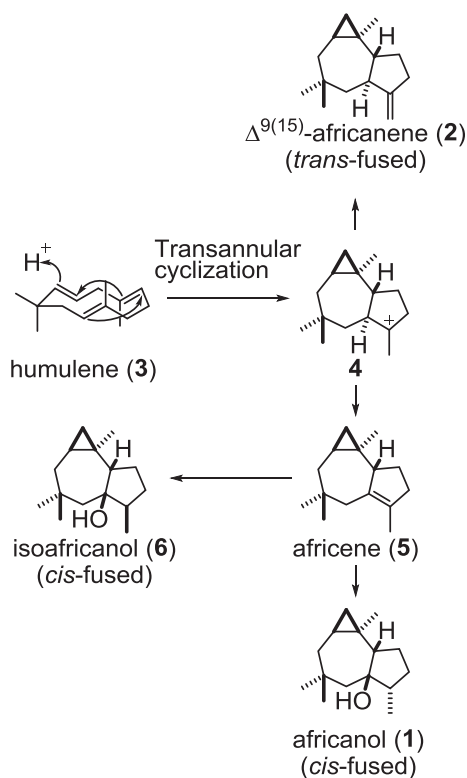
and entropic factors.⁷ Much effort aimed at the total synthesis of africanes, described in this digest, has been devoted to the formation of this seven-membered ring core. Therefore, we provide an overview of the total syntheses of africanene-type sesquiterpenoids, focusing on strategies for construction of the fused seven-membered ring structure.

Synthetic approaches to the africanene seven-membered ring system

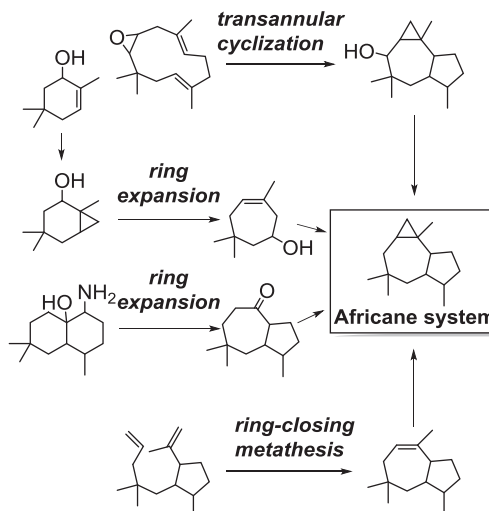
The reported strategies for construction of the africanene seven-membered ring system can be classified into three representative approaches: transannular cyclization,⁸ ring expansion,⁹ and ring closing metathesis (RCM)¹⁰ (Scheme 2). The first approach, transannular cyclization, is often observed in the terpene biosynthetic route.⁴ Although Braekman who isolated africanol (**1**) proposed a biosynthetic pathway for africanes via transannular cyclization,¹ no experimental evidence was provided. However, this hypothesis was strongly supported by Shirahama's biomimetic synthesis of africanol (**1**)¹¹ from humulene derivatives.

The second approach is ring expansion, which is widely used as the key reaction in africanene syntheses. This approach is divided into two patterns. The first is early stage construction of the cycloheptene ring from the easily formed cyclohexene ring. This methodology was first selected by Paquette and Ham.¹² They succeeded in the synthesis of africanol (**1**) using a highly stereoselective route that included ring expansion. The second pattern is a transformation from the fused 6,6 ring to the fused 5,7 ring. This methodology was reported by the Liang group¹³ using Tifeneau-Dejanov-type ring expansion. Recently, Unsworth and Taylor disclosed their synthetic approach to africanes using Cope-type ring expansion.¹⁴

The third approach is RCM. RCM is the most frequently used reaction for ring formation in the synthesis of africanes. This reliable reaction can be used for the cyclization of both *cis* and *trans* fused rings. The advent of RCM facilitated many syntheses of natural products, including the medium-sized ring of africanes. These results contributed to the development of the field of structural elucidation exemplified by Nakata's epoxyafricanene synthesis¹⁵ and Taber's *trans*-africanene-1 α -ol synthesis.¹⁶ However, their synthetic compounds were not congruent with the natural products, showing that the structures of the isolated products required revision.



Scheme 1. Proposed biosynthesis of africanes.



Scheme 2. Synthetic approaches to the africanene's seven-membered ring system.

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