Pergamon

Tetrahedron Letters 40 (1999) 5629–5632

TETRAHEDRON LETTERS

Towards the Total Synthesis of Clerocidin. Efficient Assembly of the Decalin Subunit.

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Received 21 April 1999; accepted 25 May 1999

Abstract: Decalin **14**, the fully-functionalised southern subunit of Clerocidin **1**, a unique fungal metabolite, can be readily and stereoselectively assembled from diketone **7**.

The fungal world abounds with numerous metabolites of intriguing architectural complexities and unique biological activities. Clerocidin **1**[1] and terpentecin **2**[2], isolated in 1983 from the fungus *Odiodendron truncatum*, belong to the widespread family of clerodane diterpenoids (Figure 1). These natural products, biosynthesised from geranylgeranyl pyrophosphate, exhibit potent antibacterial properties, inhibiting a broad range of Gram-positive and Gram-negative bacteria.[3] They also display interesting antitumour activities against P388 lymphocytic leukemia in mice.[4] Beside their engaging pharmacological features, clerocidin **1** and terpentecin **2** possess a rather challenging structural framework embodying a unique, highly oxygenated side-chain. This Northern fragment, which embraces a previously unknown α-keto-aldehyde functionality, may be responsible for their biological behaviour, as suggested by the poor biological performance of spirocardin B **3**.[5]

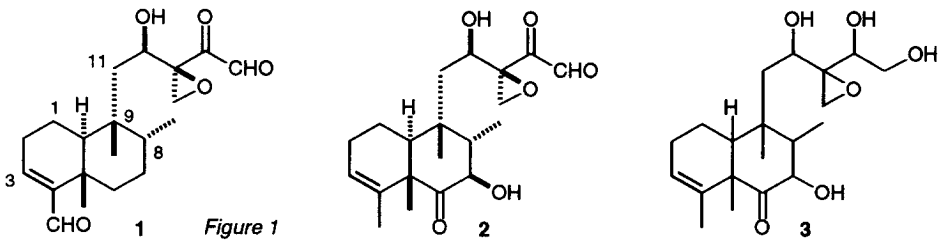

Figure 1

The intriguing activities of clerocidin **1** and terpentecin **2**, coupled with their fascinating structures, have spurred the interest of several research groups, resulting over the past years, in a number of approaches towards various portions of these natural products.[6] These sustained endeavours recently culminated in the first total synthesis of **1**.[7] Our initial involvement in the preparation of clerocidin and terpentecin led us to develop concise and highly efficient methodologies for the stereocontrolled assembly of the upper side-chain common to **1** and **2**.[8] Our antithetical analysis of clerocidin revolves around this strategy which features a Baylis-Hillman reaction,[9] coupled with an unusual, stereodirected Sharpless epoxidation[10] of an electron-deficient alkene and a final selenium dioxide oxidation (Figure 2).

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01048-5

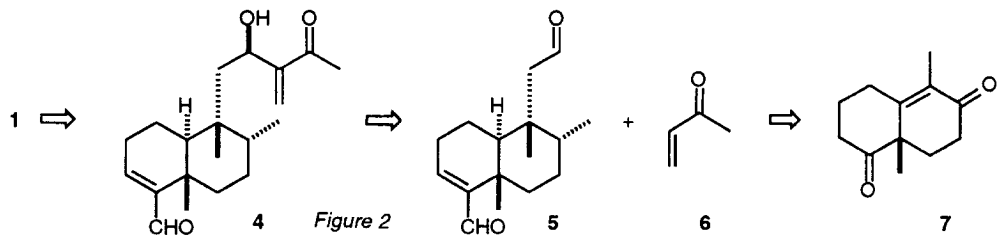

Figure 2

Accordingly, aldehyde **5** was chosen as a key-intermediate *en route* to **1** and it was envisioned that ready access to this synthon might be achieved from diketone **7**. In this article, we wish to report the successful construction of the fully functionalised decalin fragment **14** (Figure 5), ready to undergo the appendage of the highly oxygenated upper side-chain. Combined with previous work from this laboratory, the preparation of **14** also constitutes a formal total synthesis of clerocidin **1**.

Monoprotection of enone **7**,[11] using ethylene glycol and a catalytic amount of acid, afforded ketal **8** in excellent yield (Figure 3). At this stage, the establishment of the *trans* ring-junction of **9** and the concomittant incorporation of the missing C_{11}-C_{12} unit was envisaged based upon a Stork reductive-alkylation protocol.[12] However, in stark contrast to what was expected, this seemingly obvious transformation proved particularly demanding. Only under carefully controlled conditions, and **in the presence of 1 eq of H_2O**, was it possible to convert reproducibly **8** into **9**.[13]

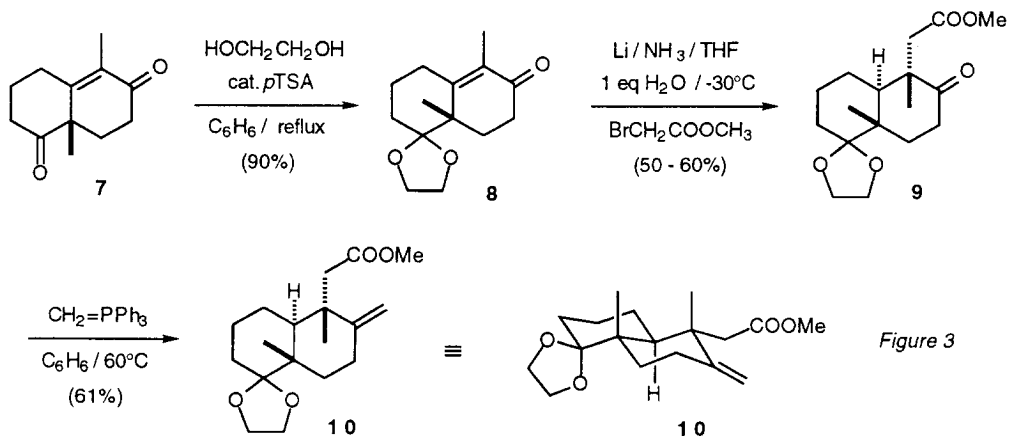

Figure 3

Remarkably, a single diastereoisomer possessing the indicated relative and absolute stereochemistry, was isolated. The location of the ester side-chain in the equatorial orientation strongly implies that the alkylation occurred on a boat-like conformer of the tetrasubstituted enolate derived from **8**, with axial approach of the α-bromoester electrophile taking place *anti* to the C_5-β-methyl substituent. This observation is consistent with previous reports on the alkylation of similarly substituted enolates.[14] Finally, Wittig olefination, under salt-free conditions,[15] afforded the *exo*-methylene decalin **10**. Essentially all of the requisite functionalities, including their correct stereochemical relationships, have been incorporated in **10** using three simple operations. At this juncture, a single chiral centre - the C_8-methyl substituent - remained to be established.

It was envisioned that the installation of this last stereocentre would be easily accomplished by catalytic hydrogenation of the exocyclic alkene present in **10**. Unfortunately, the C5- and C9-methyl substituents, both axially oriented, significantly shield the approach of the incoming reducing agent from the desired β-face. Despite extensive screening of a range of catalysts and reaction conditions, the unwanted β-isomer **11** was consistently obtained as the major product (Figure 4).

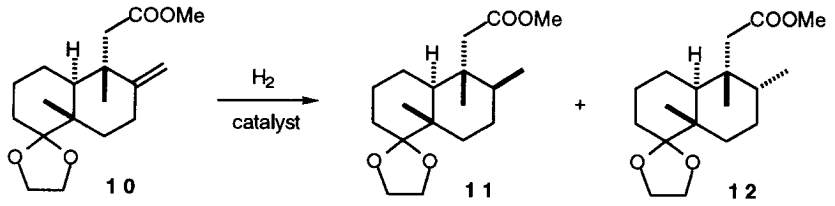

Figure 4

Gratifyingly, we discovered that Ir-black[16] promoted the addition of hydrogen from the most hindered face of substrate **10**, completely inverting the ratio of diastereoisomers **11** and **12**, in favour of the requisite α-methyl epimer. Since no special directing effects are operative in this example, the unusual selectivity displayed by Ir-black is difficult to reconcile though it remains particularly noteworthy.

The final transformation of ester **12** into aldehyde **14** proceeded smoothly and uneventfully (Figure 5).

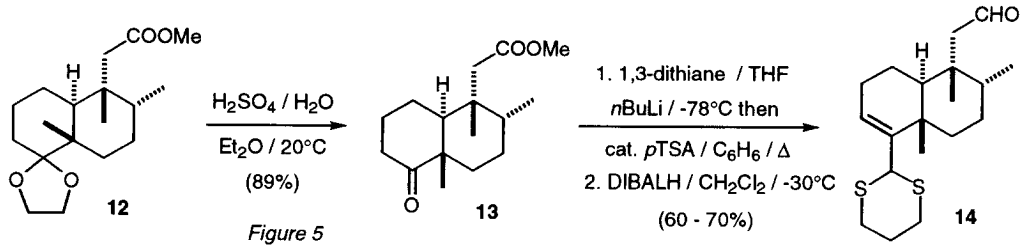

Figure 5

Thus, the cleavage of the ketal protecting group of **12** was efficiently accomplished, under mild aqueous acidic conditions, releasing the desired ketone **13**. The chemoselective addition of lithio-1,3-dithiane[17] was followed by acid-catalysed dehydration of the resulting tertiary alcohol and a DIBALH reduction, providing the long-sought after aldehyde **14** in excellent overall yield.

In summary, we have described a concise and efficient (7 steps, 20% overall yield) access to the Southern decalin fragment of clerocidin **1**. Our synthetic approach to the fully functionalised aldehyde **14** involves, as key-steps, a stereocontrolled Stork reductive-alkylation and a unique, counter-steric, iridium-catalysed hydrogenation. Efforts are now underway to complete the total synthesis of clerocidin itself. The results of these investigations will be reported in due course.

Acknowledgements.

Financial support of this work by the *Université catholique de Louvain*, the *Actions de recherche concertées* (convention 96/01-197) and the *Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture (F.R.I.A)*, in the form of a studentship to MW, is gratefully acknowledged. IEM is thankful to Merck for its continuous support and for receiving the Merck Young Investigator Award.

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