Tetrahedron 69 (2013) 9857–9864

Contents lists available at ScienceDirect

Tetrahedron

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

A novel approach to ring A analogues of the marine pyridoacridine alkaloid ascididemin

Alois Plodek, Stephan Raeder, Franz Bracher *

Department für Pharmazie—Zentrum für Pharmaforschung, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, D-81377 Munich, Germany

ARTICLE INFO

Article history:
Received 1 August 2013
Received in revised form 29 August 2013
Accepted 30 August 2013
Available online 11 September 2013

Keywords:
Alkaloids
Pyridoacridines
Homolytic acylation
Friedel–Crafts acylation
Cyclization
Trifluoromethanesulfonic acid

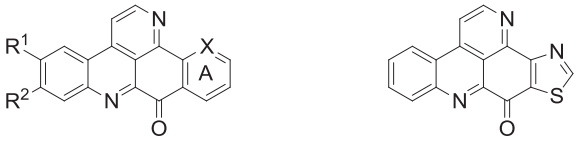
ABSTRACT

A novel approach to ring A analogues of the marine pyridoacridine alkaloid ascididemin starting from readily available 4-bromobenzo[*c*][2,7]naphthyridine (**10**) comprises a high-yield Minisci-type homolytic methoxycarbonylation at C-5, followed by introduction of the ring A scaffold via Suzuki cross-coupling reaction, and a trifluoromethanesulfonic acid-aided Friedel–Crafts-type intramolecular acylation. This protocol allows for the introduction of various electron-rich carbocyclic and heterocyclic ring A substitutes.

1. Introduction

Pyridoacridines are a unique class of alkaloids isolated from sessile marine organisms like ascidians (tunicates), sponges and bryozoa, and meanwhile more than 50 of these polycyclic heteroaromatic alkaloids have been isolated,[1–3] and based on biosynthetic considerations, a number of 'undiscovered' alkaloids of this family have been predicted.[4] Most of these alkaloids show high cytotoxicity accompanied with their DNA-binding activities, but individual, structurally even closely related pyridoacridines can vary dramatically in their molecular mechanism of cell killing.[3] Among the predominant effects are inhibition of topoisomerase II and the formation of reactive oxygen species,[2,5] in addition, induction of apoptosis has been demonstrated for ascididemin (**1**).[6] Furthermore, antibacterial, antifungal, antiviral, and insecticidal,[3] as well as antiparasitic activities against *Plasmodium*, *Leishmania*, and *Trypanosoma* species have been demonstrated.[7]

The most prominent subclass of pyridoacridine alkaloids are pentacyclic compounds derived from ascididemin (**1**; 1,8,13-triazabenzo[*fg*]naphthacen-9-one; different numberings of the ring system are used, e.g., in Ref. 3) (Fig. 1), which was isolated from the Okinawan tunicate *Didemnum* sp.[8] Though these alkaloids are available from natural sources only in trace amounts, they have been investigated thoroughly in the last two decades, since several approaches have been worked out for their total synthesis in the past (Fig. 2).



1 R^1=R^2=H, X=N
2 R^1=Br, R^2=H, X=N
3 R^1=H, R^2=OAc, X=N
4 R^1=R^2=H, X=CH

5

Fig. 1. Marine pyridoacridine alkaloids ascididemin (**1**), bromoleptoclinidinone (**2**), neocalliactine acetate (**3**), and kuanoniamine A (**5**), as well as the bioactive synthetic deaza-analogue **4**.

The first total synthesis of ascididemin (**1**) utilizing an oxidative amination of quinoline-5,8-dione, followed by acid-catalyzed cyclization and finally annulation of ring E, was worked out by one of us.[9] This methodology has later been applied to total syntheses of the related alkaloids bromoleptoclinidinone (**2**), neocalliactine

* Corresponding author. Tel.: +49 89 2180 77301; fax: +49 89 2180 77802; e-mail address: Franz.Bracher@cup.uni-muenchen.de (F. Bracher).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.08.085

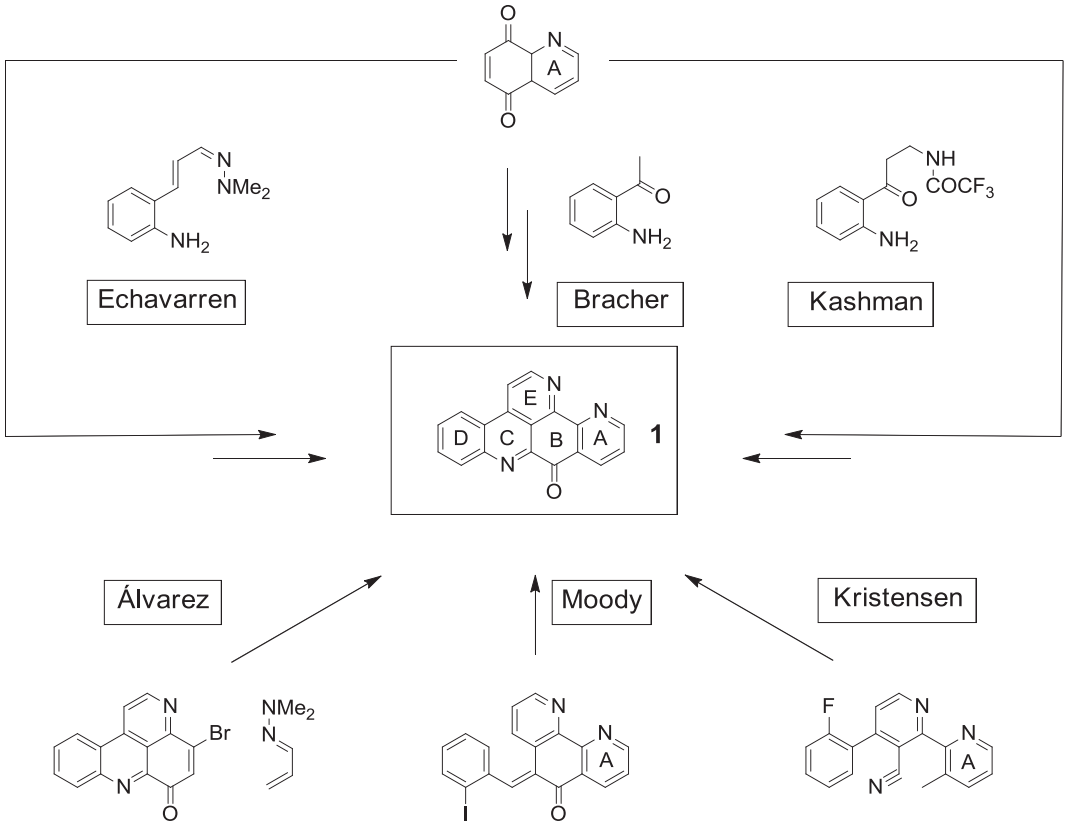


Fig. 2. Previous approaches to the alkaloid ascididemin (**1**) reported by Echavarren,[13] Bracher,[9] Kashman,[12] Álvarez,[14] Moody,[16] and Kristensen.[17]

acetate (**3**), and kuanoniamine A (**5**),[10] as well as a number of synthetic analogues[11] by us and others. Mechanistically related approaches, starting from the same quinone, were worked out by Kashman[12] and Echavarren.[13] Another synthetic approach by Álvarez et al. starts from an acridone,[14] and performs the final annulation of ring A in a hetero-Diels–Alder cycloaddition, similar to the key step performed by us earlier in the synthesis of the Annonaceae alkaloid cleistopholine.[15] Moody's total synthesis goes through a quinoneimine derived from 1,10-phenanthroline epoxide,[16] and recently, Kristensen[17] published a novel approach to **1** via anionic cascade ring closure of a phenylbipyridyl. Ciufolini et al.[18] described an approach to related alkaloids with sulfur-containing ring A by means of photochemically induced nitrene insertion reactions. Additionally, several unsuccessful approaches to ascididemin-type pyridoacridine alkaloids have been published.[19]

Significant effort has been undertaken in investigating modifications in the A ring of ascididemin (**1**) and the resulting bioactivities,[11d,14,20] and a QSAR study[21] confirmed the importance of ring A for antitumor activity. The 13-deaza derivative **4**[10,14] of **1** (also named AK37) shows reduced cytotoxicity, but in contrast to the topoisomerase II inhibitor **1** is an inhibitor of topoisomerase I, stabilizes the DNA-topoisomerase I cleavable complex, but does obviously not act through generation of reactive oxygen species.[22] Ring A analogues of **1** containing furan and thiophene rings showed significant anti-tuberculosis activity, but were not investigated further due to the complicated synthetic routes.[11d]

The observed changes in bioactivity associated with structural modifications in ring A of ascididemin (**1**) made it desirable to work out an alternative approach to ascididemin-type pyridoacridines that allows for flexible modifications in this ring by using readily available monocyclic building blocks for the introduction of this ring. The classical approach[9] is very straightforward and provides the pentacyclic ring system in four steps starting from an (aza) naphthoquinone as a ring A+B building block. However, this approach is less practical if the required bicyclic quinone has to be prepared in multistep procedures,[11d] or gives mixtures of isomers in the oxidative amination step.

Recently, we worked out a novel approach to 13-deazaascididemin (**4**), utilizing benzaldehyde as the ring A building block, but the yield of the final step (radical-induced cyclization to build up the C-13a,C-13b bond) was very poor.[23]

In this communication we report on the development of a novel approach to the pyridoacridine ring system in which readily available areneboronic acids serve as the source of ring A. The synthetic plan (Fig. 3) envisaged to start from 5-ethoxycarbonyl-4-bromobenzo[*c*][2,7]naphthyridine (**6**), which is readily available by regioselective homolytic ethoxycarbonylation of 4-bromobenzo[*c*][2,7]naphthyridine (**10**).[24a] Suzuki cross-coupling with (het) areneboronic acids should permit the introduction of various ring A equivalents, and finally, the pentacyclic (or even larger) ring system was to be constructed by intramolecular Friedel–Crafts-type acylation of the previously introduced aromatic ring.

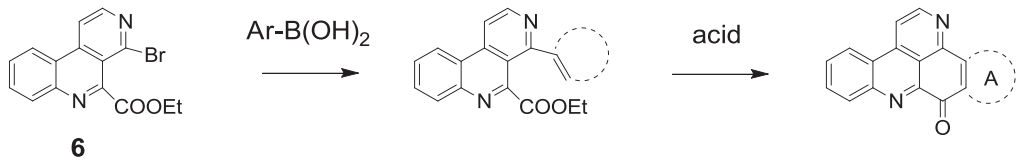


Fig. 3. New strategy for the synthesis of pyridoacridines with high variability in ring A.