## Chemical Variation of Natural-Product-Like Scaffolds: Design, Synthesis, and Biological Activity of Fused Bicyclic Acetal Derivatives\*\*

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Fused bicyclic acetals exist in many biologically active and structurally diverse natural products.<sup>[1]</sup> The knowledge that simple derivatives (1–3; Scheme 1)) function as important semio- and allelochemicals in insects and mammals,<sup>[2]</sup> coupled with the breadth of biological effects observed in more complex examples 4–11,<sup>[3–10]</sup> suggests that the fused bicyclic acetal may act as a privileged scaffold.<sup>[11]</sup> Along with biological relevance,<sup>[12]</sup> molecular diversity has become an important criteria in the selection of new frameworks for drug-discovery programs. Recently, studies into the design and synthesis of natural-product-like spiroketal derivatives as potential orally bioavailable lead compounds and probes in phenotopic screens have been reported.<sup>[13]</sup>

To extend the scope of our studies in this area, we have focused our interest on other structures such as fused bicyclic acetals. In view of the broad biological relevance of this unit, we investigated the fused bicyclic acetal as a core component by preparing a scaffold that possessed three points of appendage variation (Scheme 2). Hydroxy and acetylene groups would allow for considerable functional-group interchange, such as oxidation, followed by reductive amination or Baeyer–Villiger oxidation in the former case, and Sonogashira coupling as well as cycloaddition reactions in the latter. Furthermore, we envisaged both the cyclization step and

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Full experimental data for the preparation of all compounds except 28 may be found in the supporting information, which is available on the WWW under http://www.angewandte.org or from the author. CCDC-627561–627564 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif. rearrangement at the carbon atom of the ketal as convenient means of accessing both the 2,8- and 6,8-dioxabicyclo-



Scheme 1. Natural products that contain the fused bicyclic acetal ring system.



Scheme 2. An example of stereochemical and skeletal variation.

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[3.2.1]octane ring systems, thus providing examples of stereochemical and further skeletal change in the core component. With a small collection of suitably derivatized compounds in hand, our aim was to test their potency against a broad panel of biological targets. Herein, we report the synthesis of a series of derivatives along with some encouraging results from preliminary screening.

For the study, we used our knowledge from the synthesis of **5** (Scheme 1),<sup>[14]</sup> which employed butane-2,3-diacetal (BDA)-protected tartrate derivatives,<sup>[15]</sup> to prepare the key intermediate **16** which we anticipated would lead to the isomeric units **12–15** (Scheme 3). Retrosynthetically, we envisaged that **16** could be derived from the versatile BDA-derived nonracemic enantiopure building block **17**.



Scheme 3. Retrosynthetic analysis. TBS = tert-butyldimethylsilyl.

The route began with the elaboration of the known compound **17**. Swern oxidation and acetylide addition to the resultant aldehyde afforded **18** as a deliberate 1:1 mixture of diastereomers (Scheme 4). Efficient protecting-group manipulation subsequently led to separable diastereomeric alcohols **19 a,b** and **20 a,b**.



Scheme 4. Synthesis of the BDA-derived alcohols **19a,b** and **20a,b**. CSA = 10-camphorsulfonic acid, DME = 1,2-dimethoxyethane, DMSO = dimethyl sulfoxide, MOM = methoxymethyl, TBAF = tetra-*n*butylammonium fluoride, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

To introduce medicinally relevant groups at the  $R^1$  position, we initially chose the  $(CH_2)_2C_6H_4$ -*p*-CF<sub>3</sub> and  $(CH_2)_2C_6H_4$ -*p*-Br groups.<sup>[16]</sup> Swern oxidation of **19a,b** gave the aldehydes, which were then reacted with the phosphonate diesters **21a** and **21b** under Horner–Emmons conditions (Scheme 5).<sup>[17]</sup> The use of diverse phosphonate reagents was a convenient way to introduce chemical variation at the  $R^1$ 



Scheme 5. Synthesis of the bicyclic acetal units 12 a,b.

position of **12–15**. Reduction of the resulting enones<sup>[18]</sup> led to the precursors **16a–c**, which, on treatment with acid, cyclized to afford **12a** and **12b** as single diastereomers.<sup>[21]</sup>

From the opposite diastereomers **20** a,b, the same synthetic steps were followed for the synthesis of **16** d–f, which, when treated with acid, cyclized to form predominantly the fused bicyclic acetal units **14** a,b (Scheme 6).<sup>[19,21]</sup> Interest-



Scheme 6. Synthesis of the bicyclic acetal units 14a,b and 15a,b.

ingly, purification of **14a** or **14b** resulted in their rearrangement into **15a** and **15b**, respectively. Precedent from the literature suggests that **14a**,**b** are the kinetic products and **15a**,**b** are the thermodynamic products;<sup>[20]</sup> this proposition was reinforced by our ability to interconvert between the isomeric units **14a** and **15a** under strongly acidic conditions as an example of skeletal variation (Scheme 7).<sup>[19]</sup> The structural assignment and absolute stereochemistry of **12b** and **14b** were confirmed by X-ray analysis.

With the six structurally diverse units **12 a,b**, **14 a,b**, and **15 a,b** having been synthesized, our next aim was to transform these units into a small collection of potential biological lead



Scheme 7. Acid-catalyzed interconversion of the isomeric units 14a and 15a.

compounds. Oxidation of **12 a** to ketone **22** was achieved using Dess-Martin periodinane (DMP), while conversion of **12 a** into the corresponding triflate was followed by a base-induced elimination to afford olefin **23** (Scheme 8). The carbamates **24** and **25** were synthesized in quantitative yield using a combination of N,N'-disuccimidyl carbonate (DSC) and NEt<sub>3</sub>.



*Scheme 8.* Chemical elaboration of the bicyclic acetal **12a**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Py = pyridine.

Ketone 22 was treated with *m*CPBA to form exclusively the lactone 26 (Scheme 9). Conversion of 22 into oxime 27 and amine 28 was also possible, as was the homologative epoxidation to give the epoxide 29,<sup>[21]</sup> which could be used for further ring-opening transformations. We also explored the reactivity of the acetylene functionality of 12a, 14a,b, and 15a, and found that both Sonogashira coupling (to give 30) and triazole formation (to give 31–35) was achievable under standard conditions (Scheme 10 and 11).<sup>[21]</sup>

Given the prevalence of fused bicyclic acetals in a number of significant natural products with anticancer properties, we commenced the broad biological profiling of the compounds by evaluating their activity in cancer cells. Compounds **12a**, **24**, and **25** were examined in a primary cytotoxicity screen (72 h exposure), and IC<sub>50</sub> values (concentration required to produce 50% cell-growth inhibition) were calculated. While **12a** showed no activity (> 25  $\mu$ M for both cell lines),



*Scheme* **9.** Chemical elaboration of the bicyclic acetal **22**. HFIP=1,1,1,3,3,3-hexafluoro-2-propanol, *m*CPBA=*meta*-chloroperoxybenzoic acid, MS=molecular sieves.



Scheme 10. Further chemical elaboration of the bicyclic acetal 12a.



Scheme 11. Chemical elaboration of the bicyclic acetals 14a,b and 15a.

compound **24** gave  $IC_{50}$  values of 9.3 and 15.2 µm respectively with the MCF7 breast carcinoma and the A549 lung carcinoma cell lines; compound **25** gave values of 9.0 and greater than 25 µm. We conclude that both **24** and **25** show activity in the MCF7 line, with **25** showing selectivity compared to its relative inactivity in the A549 line. Both lines have the wildtype p53 gene, and thus the selectivity is not directly linked to p53 status.

In conclusion, a series of new fused bicyclic acetal compounds, **12a**,**b**, **14a**,**b**, and **15a**,**b**, have been synthesized. Units **12a**, **14a**,**b**, and **15a** have been elaborated into a small collection of further derivatives as potential lead com-

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pounds<sup>[22,23]</sup> (22–35) that are currently being extensively evaluated in several phenotopic screens. Preliminary screening of a small number of derivatives has already revealed some significant cytotoxic properties. Further analogues are now being prepared for screening, and the results will be reported at a later date.

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