Total Synthesis of Brevianamide A

Nat. Chem. **2020**, *12*, 615–619

"Brevianamide A, the prototypical member of the remarkable bicyclo[2.2.2]diazaoctane family of alkaloids, was isolated by Birch and Wright in 1969 and has eluded chemical synthesis ever since," said Professor Andrew L. Lawrence, University of Edinburgh (UK), introducing his group's recent major achievement: the first chemical synthesis of brevianamide A, using a biomimetic strategy. "All previous attempts to synthesise brevianamide A have only provided access to brevianamide B, a minor coisolated diastereomer (isolated d.r. of A:B in *Penicillium brevicompactum* is ≈90:10)."

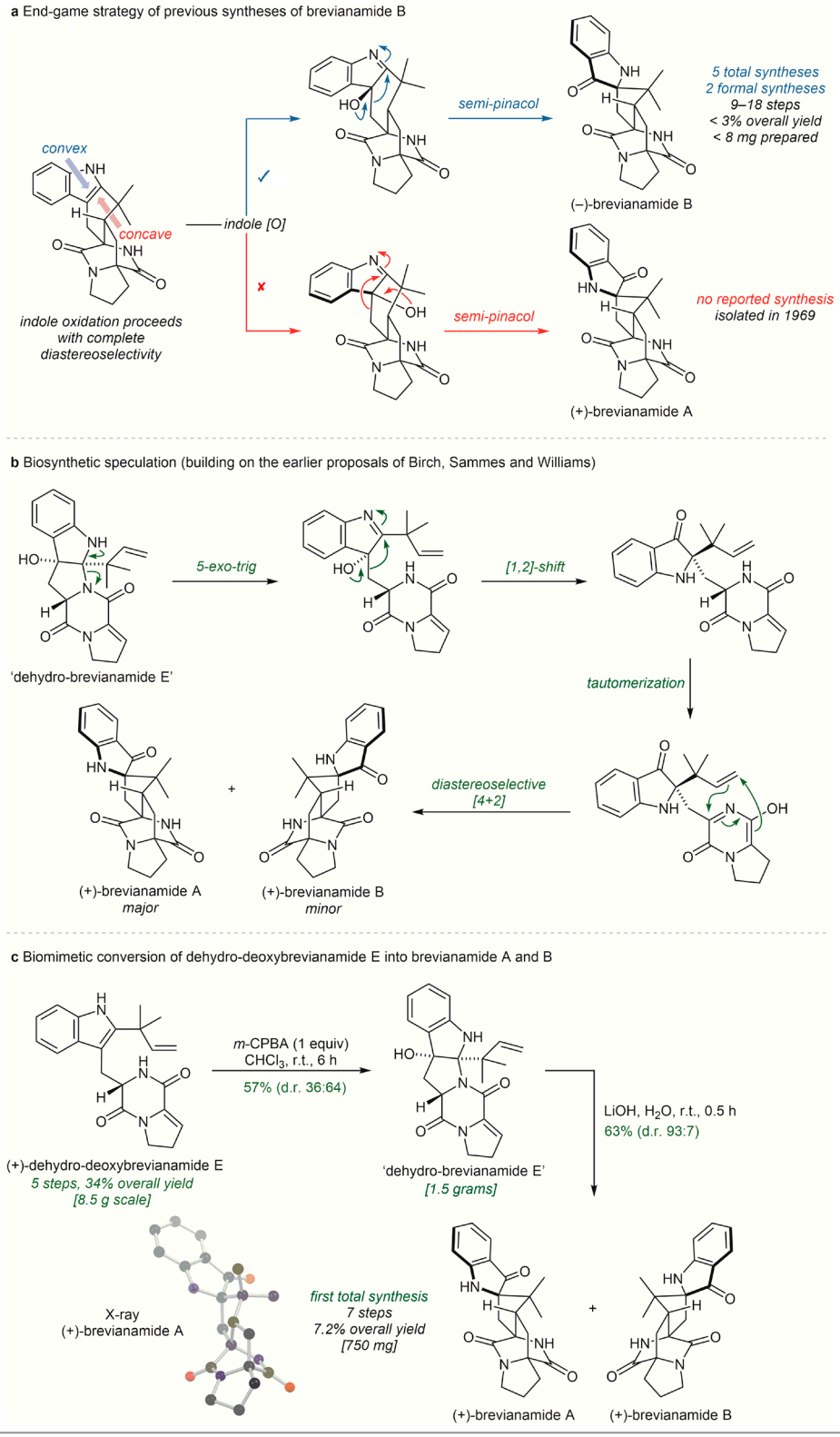
Professor Lawrence's group have long been interested in developing biomimetic synthetic strategies towards complex natural products. "This bio-inspired approach facilitates the design of short, efficient syntheses that provide opportunities to test the chemical feasibility of proposed biosynthetic pathways," added Professor Lawrence, who went on to explain: "Brevianamide A could not be accessed previously because all other approaches featured a common 'end-game' strategy of indoleoxidation and semipinacol rearrangement (Scheme 1a). Unfortunately, late-stage oxidation of the polycyclic indole intermediate exhibits exclusive selectivity for the convex face of the indole, which following stereospecific semi-pinacol rearrangement leads to brevianamide B. Thus, it was clear that a fundamentally different approach was required if we wanted to access brevianamide A."

Dr. Robert Godfrey, a PhD student in the Lawrence group at the time, had prepared the natural product dehydro-deoxybrevianamide E on large scale during attempts to access some related natural products. "After studying the reactivity of this versatile intermediate in great detail, we began to suspect that its oxidation product, 'dehydro-brevianamide E' might be a key (bio)synthetic precursor to brevianamide A," explained Dr. Godfrey (Scheme 1b).

The authors were delighted to observe that simply treating 'dehydro-brevianamide E' with aqueous base gave direct conversion into brevianamides A and B (Scheme 1c), presumably via their proposed biomimetic domino retro-5-*exo*-*trig*/semi-pinacol/tautomerization/Diels–Alder reaction sequence (Scheme 1b). Remarkably, the diastereomeric ratio observed from the reaction in the laboratory (d.r. 93:7) matched closely with the ratio obtained when these alkaloids are isolated from the fungus. EPSRC-funded Postdoctoral Research Associate, Dr. Nicholas Green explained: "Although *Diels–Alderase* enzymes are known to be involved in the biosynthesis of related bicyclo[2.2.2]diazaoctane alkaloids, our results suggest that a *Diels–Alderase* enzyme is not required to explain the stereochemical outcome in the biosynthesis of the brevianamides." Dr. Robert Godfrey added: "It was particularly rewarding to see our proposal of a *Diels–Alderase*-free biosynthesis was later supported by a beautifully detailed biosynthetic study reported by Williams, Sherman, Li and co-workers (*Nat. Catal.* **2020**, *3*, 497–506)."

When asked about the future of the field, Professor Lawrence responded, "There has been a tremendous amount of progress on studying the structure, synthesis, origins, and function of these amazing alkaloids, most notably by the group of Professor Robert M. Williams at Colorado State University. There are, however, many important questions and synthetic challenges that remain to be answered, which should continue to attract new researchers to the field. I wrote to Professor Williams last year to inform him of our work. I was a little apprehensive about reaching out; we chemists can sometimes be rather territorial. I needn't have worried, in his response he very kindly and warmly wrote "*Congratulations on a really outstanding and brilliant synthesis of Brevianamides A and B! This is very exciting*". Without his great body of work on these fascinating natural products our total synthesis would have never happened."

Professor Lawrence concluded: "We were shocked and very sad to hear of Professor Williams' death on 13th May 2020, and we dedicate this work to his memory."


a End-game strategy of previous syntheses of brevianamide B
convex
concave
indole oxidation proceeds with complete diastereoselectivity
indole [O]
semi-pinacol
5 total syntheses
2 formal syntheses
9–18 steps
< 3% overall yield
< 8 mg prepared
(–)-brevianamide B
semi-pinacol
no reported synthesis
isolated in 1969
(+)-brevianamide A
b Biosynthetic speculation (building on the earlier proposals of Birch, Sammes and Williams)
'dehydro-brevianamide E'
5-exo-trig
[1,2]-shift
tautomerization
diastereoselective
[4+2]
(+)-brevianamide A
major
(+)-brevianamide B
minor
c Biomimetic conversion of dehydro-deoxybrevianamide E into brevianamide A and B
(+)-dehydro-deoxybrevianamide E
5 steps, 34% overall yield
[8.5 g scale]
m-CPBA (1 equiv)
CHCl3, r.t., 6 h
57% (d.r. 36:64)
'dehydro-brevianamide E'
[1.5 grams]
LiOH, H2O, r.t., 0.5 h
63% (d.r. 93:7)
X-ray
(+)-brevianamide A
first total synthesis
7 steps
7.2% overall yield
[750 mg]
(+)-brevianamide A
(+)-brevianamide B

Scheme 1

About the authors

Dr. R. C. Godfrey

Robert C. Godfrey was born in Sweden and received his BSc degree from University of Cambridge (UK) in 2014. He completed his PhD in 2019 under the supervision of Professor Andrew L. Lawrence at the University of Edinburgh (UK) and rejoined the group as a Postdoctoral Research Associate in the same year. His research is focused on the biomimetic synthesis of the brevianamides and related prenylated indole alkaloids.

Dr. N. J. Green

Nicholas J. Green completed his PhD studies as a Rod Rickards Scholar with Professor Michael S. Sherburn at the Australian National University (Australia) before undertaking postdoctoral research with Professor Andrew L. Lawrence at University of Edinburgh (UK), and is now working with Dr. John Sutherland at the MRC Laboratory of Molecular Biology in Cambridge (UK). Nick's background is in organic synthesis spanning transition-metal and organic catalysis, total synthesis, and biomimetic chemistry, and he is now investigating the origins of life.

Professor A. L. Lawrence

Andrew L. Lawrence completed his undergraduate studies at the University of Oxford (UK) in 2006 (MChem, Hons 1st Class) and subsequently obtained a DPhil degree in 2010 under the supervision of Professor Sir Jack E. Baldwin FRS and Dr. Robert M. Adlington. He then spent two years (2010–2011) as a Postdoctoral Research Associate with Professor Michael S. Sherburn at the Australian National University (ANU) in Canberra (Australia). In 2012, he began an Australian Research Council DECRA Fellowship at the ANU before moving back to the UK in late 2013 for a Lectureship position at the University of Edinburgh (UK). He was promoted to Senior Lecturer in 2017 and Full Professor in 2020.

© Georg Thieme Verlag Stuttgart • New York – Synform **2020/11**, A160–A162 • Published online: October 20, 2020 • DOI: 10.1055/s-0039-1691213