Asymmetric Synthesis

DOI: 10.1002/anie.200503374

Short, Enantioselective Total Synthesis of Sceptrin and Ageliferin by Programmed Oxaquadricyclane Fragmentation**

Phil S. Baran, Ke Li, Daniel P. O'Malley, and Christos Mitsos*

Dedicated to Professor David I. Schuster on the occasion of his 70th birthday.

The marine-derived dimeric pyrrole-imidazole alkaloids sceptrin (1) and ageliferin (2) are endowed with intriguing molecular architectures and a range of useful bioactivities (Scheme 1).^[1] The enantioselective synthesis of a dimeric pyrrole-imidazole alkaloid has yet to be reported, partly because of the intrinsic difficulty associated with handling multiply charged nitrogen-containing intermediates.^[2]

We recently described practical syntheses of both 1 and 2 in their racemic form^[3,4] by the use of an oxaquadricyclane fragmentation to generate the cyclobutane core of 1. Since the mechanism of this reaction remained ill-defined,^[5] it was unclear how, or even if, stereochemical information in an oxaquadricyclane could be transferred to the product cyclobutane. Indeed, preliminary screens using numerous enantioenriched oxaquadricyclanes (3, Scheme 2) under a variety of acidic conditions led to cyclobutanes which were either racemic or showed a considerable loss of optical activity. Racemic oxaquadricyclanes were also evaluated with chiral acids and auxiliaries, but to no avail. Further investigation was warranted because of the lack of viable alternatives for the enantioselective synthesis of tetrasubstituted cyclobutanes.^[6]

Herein, we report the details of a unique method for the enantioselective synthesis of tetrasubstituted cyclobutanes by programmed fragmentation of an oxaquadricyclane, and the

 [*] Prof. Dr. P. S. Baran, Dr. K. Li, D. P. O'Malley, Dr. C. Mitsos Department of Chemistry The Scripps Research Institute
 10550 North Torrey Pines Road, La Jolla, California 92037 (USA) Fax: (+1) 858-784-7375
 E-mail: pbaran@scripps.edu

[**] We thank Dr. D. H. Huang and Dr. L. Pasternack for NMR spectroscopic assistance, and Dr. G. Siuzdak and Dr. R. Chadha for mass spectrometric and X-ray crystallographic assistance, respectively. We are grateful to Biotage for a generous donation of microwave process vials that were used extensively during these studies and to the Department of Defense and the Hertz Foundation for pre-doctoral fellowships (D.P.O.). Financial support for this work was provided by The Scripps Research Institute, Amgen, Dupont, Eli Lilly, GlaxoSmithKline, Roche, the Searle Scholarship Fund, and NIH/NIGMS (GM-073949).

Supporting information for this article (detailed experimental procedures, copies of all spectral data, and full characterization) is available on the WWW under http://www.angewandte.org or from the author.





Scheme 1. The structures of sceptrin (1) and ageliferin (2). TFA=trifluoroacetate.



Scheme 2. Unsuccessful attempts at enantioselective fragmentation of an oxaquadricyclane.

application of this method to the first asymmetric synthesis of both enantiomers of sceptrin and ageliferin.

The synthesis commenced with the enzymatic desymmetrization^[7] of meso-diester 4^[3a] using pig liver esterase (PLE) to provide monoester 5 in quantitative yield and 75% ee (Scheme 3). The ee value was determined by ¹H NMR spectroscopic analysis of the amide derived from (S)- α methylbenzylamine (absolute configuration determined by X-ray analysis of the ammonium salt derived from the same amine and 5). Formation of a benzylamide using DMT-MM^[8] afforded the monobenzylamide 6 in 92% yield. Remarkably, cis,trans,trans-cyclobutane 10 was formed in 50% overall yield and 75% ee when amide 6 was irradiated to form oxaquadricyclane 7 and directly treated with H₂SO₄ in THF/ MeOH (1:1). Amide (-)-10 is nearly enantiopure (>95% ee)after a single recrystallization. The use of a benzylamide was critical to achieve complete transfer of chirality. A mild and chemoselective debenzylation/esterification of the robust secondary amide in 10 and epimerization to the all-trans stereochemistry were necessary to access (-)-13. Treatment of 10 with TsOH and MeOH in toluene at 105°C^[9] accomplished all three tasks in a single pot to afford (-)-13in 90% yield. The ease with which this amide is hydrolyzed is likely due to assistance by the nearby cis-methyl ketone, as depicted in structure 12 (simple secondary amides are not converted into methyl esters under these conditions).



Communications



Scheme 3. Enantioselective Synthesis of *ent*-1 and *ent*-2. Reagents and conditions: a) PLE (50 unit mmol⁻¹), acetone/phosphate buffer (pH 8), 23 °C, 1 week, 100%, 75% *ee*; b) BnNH₂ (1.05 equiv), DMT-MM (1.05 equiv), THF, 3 h, 92%; c) *hv*, THF, 72 h, then H₂SO₄, THF/ MeOH (1:1), 3 h, 45–50%; d) recrystallization from hexanes/EtOAc (1:1), then TsOH (4.0 equiv), MeOH (20 equiv), toluene, 105 °C, sealed tube, 12 h, 50%. Bn = benzyl, THF = tetrahydrofuran; TsOH = toluene-sulfonic acid, DMT-MM =4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride.

The absolute configuration of (-)-13 was verified by conversion into sceptrin^[3a] and comparison with a natural sample, which revealed that *ent*-sceptrin (1) had been synthesized ($[\alpha]_D = +16.0$ (MeOH, c = 0.25, HCl salt), lit. [1] $[\alpha]_D = -7.4$ (MeOH, c = 1.2, HCl salt)). Exposure of *ent*-sceptrin (1) to microwave irradiation^[3b] led to *ent*-ageliferin (2; $[\alpha]_D = +8.0$ (MeOH, c = 0.05, TFA salt), natural product $[\alpha]_D = -10.0$ (MeOH, c = 0.1, TFA salt)).^[3] The absolute configuration of 2 can now be assigned as depicted in Scheme 1.

The naturally occurring forms of 1 and 2 could be prepared as outlined in Scheme 4. Thus, monoacid 5 was



Scheme 4. Enantioselective Synthesis of *nat*-1 and *nat*-2. Reagents and conditions: a) 1. DMT-MM (1.05 equiv), DMAP (0.05 equiv), *i*PrOH, 55 °C, 3 h; 2. LiOH (1.2 equiv), THF/H₂O (1:1), 2 h; 3. DMT-MM (1.05 equiv), BnNH₂ (1.05 equiv), THF, 3 h, 80% (3 steps); b) *hv*, THF, 72 h, then H₂SO₄, THF/MeOH (1:1), 3 h, 45–50%; c) recrystallization from hexanes/EtOAc (1:1), then *p*TsOH (4.0 equiv), MeOH (20 equiv), toluene, 105 °C, sealed tube, 12 h, 50%. DMAP=4-dimethylaminopyridine.

directly converted into the amide 14 in 80% overall yield, without purification, by sequential formation of an ester, selective saponification of the methyl ester, and formation of an amide. Amide 14 was amenable to the same reaction sequence used for 6 (Scheme 3) and furnished cyclobutane 17 with complete conservation of optical activity. Following recrystallization (>95% ee), epimerization, and transesterification to (+)-13, the synthesis of nat-(-)-sceptrin ([α]_D = -11.7 (MeOH, c = 0.12, HCl salt)) and (-)-ageliferin ($[\alpha]_{D} =$ -10.0 (MeOH, c = 0.03, TFA salt)) was completed. Both the sign and magnitude of the optical rotation of sceptrin changes depending on the counteranion (synthetic ent-sceptrin bishydrochloride had $[\alpha]_{\rm D} = +16.0$ (MeOH, c = 0.25, HCl salt), while the bistrifluoroacetate salt had $[\alpha]_{\rm D} = -23.5$ (MeOH, c = 0.75, no literature value available). This unusual reversal of optical rotation and the fact that the literature measurements for 1 and 2 are variable necessitated the use of circular dichroism to verify the assignments (Figure 1). The fact that (-)-2 can be derived from (-)-1 is consistent with the suggestion that the former may be produced from the latter in nature or that they share common intermediates in the biosynthetic pathway.^[2,3b]

The cascade rearrangement of oxaquadricyclanes to cyclobutanes was initially discovered by McInnes and coworkers,^[5a] who proposed a mechanism involving the initial fragmentation of the oxa bridge with water. The cascade was



Figure 1. Top: Circular dichroism (CD) spectra of natural (-)-sceptrin (green), synthetic (-)-sceptrin (blue), and synthetic (+)-sceptrin (red) in water (0.2 mm). Bottom: Circular dichroism (CD) spectra of natural (-)-ageliferin (green), synthetic (-)-ageliferin (red), and synthetic (+)-ageliferin (blue) in water (0.35 mm). All measurements were recorded at 25 °C.

later studied by Nelsen and Calabrese,^[5b] who posited an alternative mechanism initiated by fragmentation of a cyclopropyl ring to form an oxocarbonium ion (see 8 and 16). After the work of Nelsen and Calabrese, little notice was taken of this reaction until it was adopted in the synthesis of sceptrin.^[3] Success of an enantioselective variant relied on the assumption that the configuration of the final product is controlled by the order of the enolization (or protonation) of the carbonyl groups in the first fragmentation. For example, the major enantiomer (10) resulting from the fragmentation of 7 is produced by initial enolization of the benzylamide (Scheme 3), whereas the minor enantiomer (ent-10) would be produced by initial enolization of the ester. This result fits with the results of theoretical predictions that have found that enols of amides are more stable than those of carboxylic acids or esters.^[10] The selective fragmentation of 7 to amide enol 8 is followed by tautomerization (protonation from the convex face) and capture by water to furnish 9. Immediate fragmentation leads to the stable *cis,trans,trans*-cyclobutane 10. The efficiency and complete transfer of chirality observed in these reactions ($6 \rightarrow 10$ and $14 \rightarrow 17$) is surprising given the complexity of this mechanism, the difficulties encountered at the outset (see above), and the fact that oxaguadricyclanes are prone to a variety of other rearrangements under acidic conditions.^[5c] This method proceeds in an operationally simple, scalable, and direct manner and represents the first solution for the nontrivial problem of the enantioselective construction of a tetrasubstituted cyclobutane which does not rely upon chiral auxiliaries.^[6,11]

In summary, the first enantioselective syntheses of the dimeric pyrrole-imidazole alkaloids sceptrin (1) and ageliferin (2) have been accomplished (18% overall for (-)-1 from commercially available compounds). Notably, column chromatography (on 10 and 17) and HPLC (to separate 1 from 2) only need to be performed once during the entire sequence. These syntheses have enabled the assignment of the absolute configuration of 2, provided insight into the mechanism of the remarkable oxaquadricyclane \rightarrow cyclobutane rearrangement, and opened up an enantioselective route to other complex alkaloids in this family.^[12]

Received: September 23, 2005 Published online: November 30, 2005

Keywords: asymmetric synthesis · cascade reactions · enantioselectivity · natural products · rearrangement

- a) Sceptrin: R. P. Walker, D. J. Faulkner, D. Van Engen, J. Clardy, J. Am. Chem. Soc. **1981**, 103, 6772-6773; b) Ageliferin: P. A. Keifer, R. E. Schwartz, M. E. S. Koker, R. G. Hughes, Jr., D. Rittschof, K. L. Rinehart, J. Org. Chem. **1991**, 56, 2965-2975.
- [2] For reviews, see H. Hoffmann, T. Lindel, Synthesis 2003, 1753– 1783; D. E. N. Jacquot, T. Lindel, Current Org. Chem. 2005, 9, 1551–1565.
- [3] a) P. S. Baran, A. L. Zografos, D. P. O'Malley, J. Am. Chem. Soc.
 2004, 126, 3726-3727; b) P. S. Baran, D. P. O'Malley, A. L.
 Zografos, Angew. Chem. 2004, 116, 2728-2731; Angew. Chem. Int. Ed. 2004, 43, 2674-2677.
- [4] For a recent synthesis of (±)-1, see V. B. Birman, X.-T. Jiang, Org. Lett. 2004, 6, 2369-2371; for studies toward 2, see Ref. [2] and Y. He, Y. Chen, H. Wu, C. J. Lovely, Org. Lett. 2003, 5, 3623-3626; I. Kawasaki, N. Sakaguchi, N. Fukushima, N. Fujioka, F. Nikaido, M. Yamashita, S. Ohta, Tetrahedron Lett. 2002, 43, 4377-4380.
- [5] a) J. Laing, A. W. McCulloch, D. G. Smith, A. G. McInnes, *Can. J. Chem.* 1971, 49, 574-582; b) S. F. Nelsen, J. C. Calabrese, J. Am. Chem. Soc. 1973, 95, 8385-8388; c) for a review of oxaquadricyclane chemistry, see W. Tochtermann, G. Olsson, *Chem. Rev.* 1989, 89, 1203-1214.
- [6] The use of chiral auxiliaries in [2+2] cycloadditions was shown to be only partially stereoselective with cinnamate derivatives, see D. Haag, H.-D. Sharf, J. Org. Chem. 1996, 61, 6127–6135; for a review, see E. Lee-Ruff, G. Mladenova, Chem. Rev. 2003, 103, 1449–1483.
- [7] a) M. Ohno, Y. Ito, T. Shibata, K. Adachi, H. Sawai, *Tetrahedron* 1984, 40, 145–151; b) R. Bloch, E. Guibe-Jampel, C. Girard, *Tetrahedron Lett.* 1985, 26, 4087–4090; for a review of *meso* compounds in synthesis, see R. Hoffmann, *Angew. Chem.* 2003, 115, 1128–1142; *Angew. Chem. Int. Ed.* 2003, 42, 1096–1109.
- [8] 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride: M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki, S. Tani, *Tetrahedron* **1999**, *55*, 13159–13170.
- [9] C.-Y. Chern, Y.-P. Huang, W. M. Kan, *Tetrahedron Lett.* 2003, 44, 1039–1041.

Communications

- [10] N. Heinrich, W. Koch, G. Frenking, H. Schwarz, J. Am. Chem. Soc. 1986, 108, 593–600; R. E. Rosenberg, J. Org. Chem. 1998, 63, 5562–5567.
- [11] For an example of a cyclobutane with vicinal quaternary centers(18) that can be made using this method, see the Supporting Information.



[12] CCDC-281469 (chiral ammonium salt of 5) contains 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.