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Synthesis of Sceptrin Alkaloids

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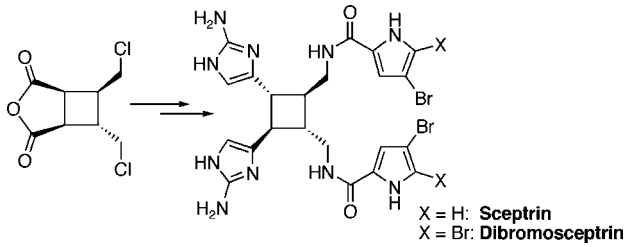
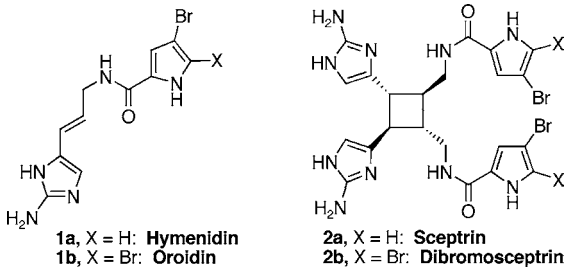
ABSTRACT



A concise synthetic route to the marine alkaloids (±)-sceptrin and (±)-dibromosceptrin has been developed.

The growing family of pyrrole-imidazole alkaloids continues to provide the synthetic community with exciting targets.[1] The biosynthesis of these marine natural products from simple parent compounds such as hymenidin (**1a**) and oroidin (**1b**) is fascinating in itself, given their extreme structural diversity and complexity.[2] In addition, many of these compounds are pharmacologically active.[1] We have become particularly interested in sceptrin (**2a**)[3] and related alkaloids (e.g., dibromosceptrin **2b**[3b]) for two reasons. First, sceptrin exhibits a broad range of biological activities. In addition to its antibacterial, antiviral,[3b] antimuscarinic,[4] and antihistaminic[5] properties, sceptrin is a somatostatin inhibitor in the submicromolar range.[6] Furthermore, its modular architecture makes it an ideal starting point for structural modification in search of pharmacologically useful synthetic analogues. Second, we have envisioned a synthetic route to the more complex axinellamine alkaloids[7] based on the cyclobutane ring expansion of dibromosceptrin via a cationotropic 1,2-shift.[8b,9]



With this in mind, we have developed a concise and flexible synthetic route to (±)-sceptrin and (±)-dibromosceptrin presented below. While this work was in progress, the first total synthesis of sceptrin by Baran et al. appeared in the literature.[8a]

(1) For a review, see: Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753.

(2) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.

(3) (a) Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772. (b) Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G., Jr.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965.

(4) Rosa, R.; Silva, W.; Escalona de Motta, G.; Rodriguez, A. D.; Moralez, J. J.; Ortiz, M. *Experientia* **1992**, *48*, 885.

(5) Cafieri, F.; Carnuccio, R.; Fattorusso, E.; Taglialatela-Scafati, O.; Vallefuoco, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2283.

(6) Vassas, A.; Bourdy, G.; Paillard, J. J.; Lavayre, J.; Pais, M.; Quirion, J. C.; Debitus, C. *Planta Med.* **1996**, *62*, 28.

(7) Urban, S.; Leone, P. de A.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731.

(8) (a) Baran, P. S.; Zografos, A. L.; O'Malley, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 3726. (b) During the review of this manuscript, Baran et al. proposed a biosynthetic transformation of sceptrin into axinellamine A similar to our synthetic plan: Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674.

(9) For studies towards axinellamines, see: (a) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793. (b) Dransfield, P. J.; Wang, S.; Romo, D. *Abstracts of Papers*, 227th National Meeting of the American Chemical Society, Anaheim, CA, Mar 28−Apr 1, 2004; American Chemical Society: Washington, DC, 2004; ORGN 399.

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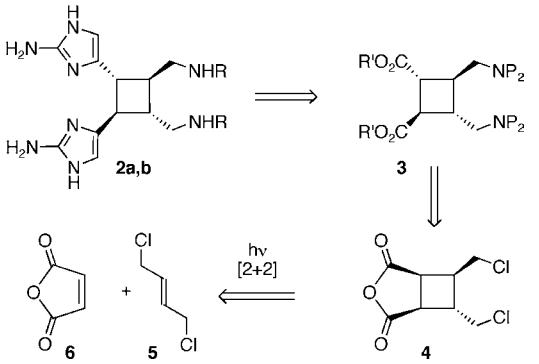
Scheme 1. Retrosynthetic Analysis of the Sceptrin Skeleton

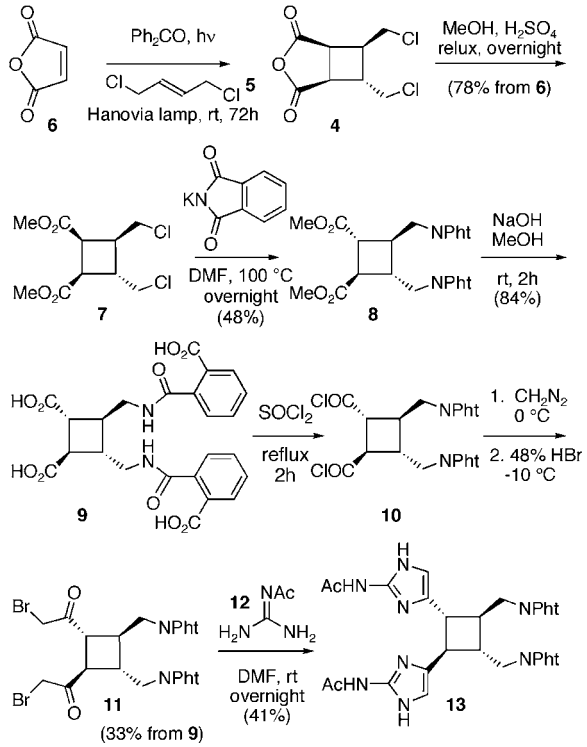


Our retrosynthetic analysis is shown in Scheme 1. Although in principle the sceptrin skeleton can be assembled by the photodimerization of urocanic esters,[10] in a fashion reminiscent of its biosynthesis, we chose to use a "nonbiogenetic" disconnection for its synthesis that took advantage of the known photocycloaddition of maleic anhydride to *trans*-1,4-dichloro-2-butene.[11] The "unnatural" stereochemistry of the initial photoadduct **4** could potentially be adjusted during the course of the synthesis by epimerization to the thermodynamically more stable all-trans configuration.

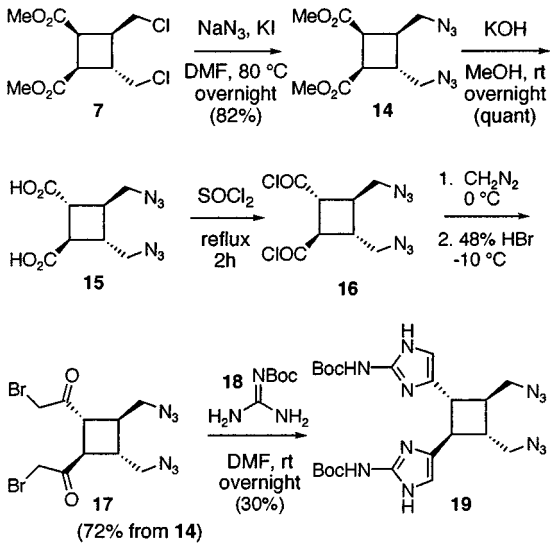
Our original synthetic plan relied on the Gabriel synthesis to install the protected amino groups. Accordingly, we prepared photoadduct **4** and converted it into the dimethyl diester **7** using a modified literature procedure[11] (Scheme 2). Reaction of the diester with potassium phthalimide in DMF was accompanied by epimerization and gave the all-trans product **8** directly. Base hydrolysis of the carbomethoxy groups in **8** was invariably accompanied by the ring opening of the phthalimide moieties. Fortunately, the resulting tetraacid **9** recyclized after treatment with thionyl chloride, giving the bis-acyl chloride **10**. Reaction with excess diazomethane followed by hydrobromic acid gave the desired bis-bromomethyl ketone **11**. The 2-aminoimidazole moieties were installed using the known reaction with *N*-acetylguanidine **12**.[12]

Further development of this sequence was hampered by the low solubility of phthalimide-containing compounds in all solvents except DMSO. In addition, selective hydrolysis of either the acetyl groups or the phthalimide moieties proved to be problematic. These issues were addressed in the second-generation approach (Scheme 3).

Scheme 2. First-Generation Approach to Sceptrin



Scheme 3. Second-Generation Approach



Treatment of dimethyl diester **7** with sodium azide occurred without significant epimerization and gave **14** in high yield. The required all-trans stereochemistry was attained in the next step, during the base hydrolysis to the diacid (**15**). Overall, the conversion of diester **14** into bis-bromomethyl ketone **17** proceeded in a much better overall yield than the analogous transformation of **8** to **11** (72 vs 28%).

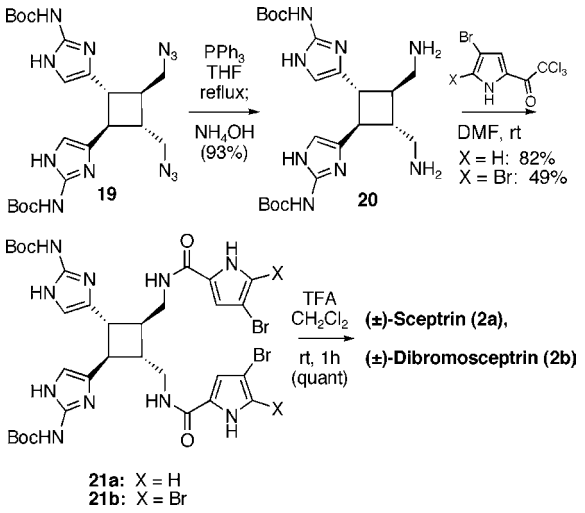
Completion of the total syntheses of sceptrin and dibromosceptrin required a reliable and mild method of deprotecting the 2-aminoimidazole moiety. Therefore, the literature method for preparation of 2-aminoimidazoles[12] was modified by replacing *N*-acetylguanidine **12** with its *tert*-butoxycarbonyl counterpart (**18**).[13] Treatment of bis-bromomethyl

(10) D'Auria, M.; Racioppi, R. *J. Photochem. Photobiol. A* **1998**, *112*, 145.
(11) Wissner, A.; Meinwald, J. *J. Org. Chem.* **1973**, *38*, 1697.
(12) Little, T. L.; Webber, S. E. *J. Org. Chem.* **1994**, *59*, 7299.
(13) *N*-Boc-guanidine was prepared as previously described: Buchinska, T. V. *J. Pept. Res.* **1999**, *53*, 314.

ketone **17** with this reagent proceeded in 30% (unoptimized) yield to give the orthogonally protected sceptrin precursor **19**.

Reduction of the azide groups was best achieved by treatment with triphenylphosphine in refluxing THF and subsequent hydrolysis with aqueous ammonia (Scheme 4).

Scheme 4. Preparation of Sceptrin and Dibromosceptrin



The resulting diamine (**20**) was acylated with 2-trichloroacetyl-4-bromopyrrole[14] in DMF to afford bis-Boc-protected sceptrin **21a**. Removal of the Boc groups with TFA gave (±)-sceptrin bis-trifluoroacetate in a quantitative yield. In an analogous fashion, treatment of **20** with 2-trichloroacetyl-4,5-dibromopyrrole[15] gave **21b**. Subsequent deprotection produced (±)-dibromosceptrin bis-trifluoroacetate. Spectral data of both natural products thus obtained were in agreement with those reported earlier.[3,8a,16]

In conclusion, we have developed a concise and versatile synthetic route to the sceptrin alkaloids. Although still unoptimized, the present sequence affords sceptrin and dibromosceptrin in 10.5 and 6.3% overall yields, respectively, and is easily amenable to scaleup. The strategy disclosed herein is expected to provide rapid access to a variety of derivatives and analogues of these natural products and to facilitate the development of the biogenetically inspired synthetic route to axinellamines.

Acknowledgment. This study was sponsored by Washington University in St. Louis.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Kitamura, C. and Yamashita, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1443.

(15) Behrens, C.; Christoffersen, M. W.; Gram, L.; Nielsen, P. H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 321. Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300.

(16) Identity of (±)-sceptrin obtained in these studies was confirmed by comparison with ^{1}H spectra of the natural and synthetic samples of sceptrin·2HCl reported by Baran et al.[8a] ^{1}H NMR data for synthetic (±)-dibromosceptrin·2HOAc were identical to those reported for the natural product by Rinehart et al.[3b] All ^{13}C NMR data of synthetic dibromosceptrin·2HOAc were identical to those of the natural compound except for a carbon at 129.7 ppm, compared to 128.7 ppm reported by Rinehart, et al.[3b] ^{13}C NMR chemical shifts were found to be concentration-dependent, and up to 0.5 ppm differences were observed at different concentrations.