ORGANIC LETTERS

2008
Vol. 10, No. 18
4001−4003

N,N-Acetals as *N*-Acyliminium Ion Precursors: Synthesis and Absolute Stereochemistry of Epiquinamide

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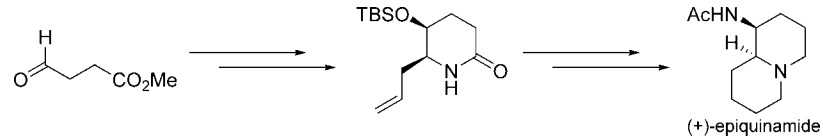
Received July 1, 2008

ABSTRACT



A stereoselective synthesis of (+)-epiquinamide is presented in combination with determination of the absolute configuration of the natural product. Key steps in the sequence involved chemoenzymatic formation of an enantiomerically pure cyanohydrin, reductive cyclization to the corresponding cyclic *N,N*-acetal, and subsequent conversion into a suitable *N*-acyliminium ion precursor to enable construction of the second ring.

N-Acyliminium ions are versatile intermediates for the synthesis of heterocyclic structures and alkaloid natural products.[1] The generation of the highly reactive cationic *N*-acyliminium species typically relies on (i) (Lewis) acidic treatment of *N,O*-acetals, (ii) protonation of enamides,[2] or (iii) electrochemical oxidation of acylated amines.[3] This article details an unprecedented strategy to form *N*-acyliminium ions based on the ready availability of functionalized cyclic *N,N*-acetals. Besides providing the first example of this conversion, it was also used as a key transformation in a total synthesis of (+)-epiquinamide (**1**). Epiquinamide was isolated in 2003 from the poison frog *Epipedobates tricolor* by Daly and co-workers and was claimed to act as an agonist

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(1) For excellent reviews, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (c) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.

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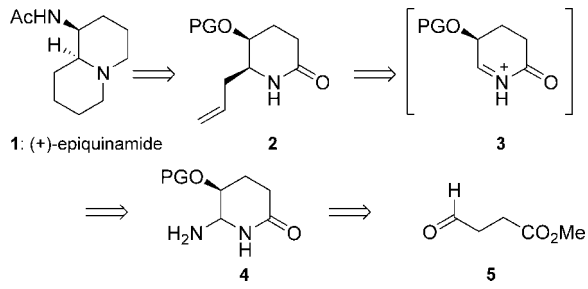
10.1021/ol801490m CCC: $40.75 © 2008 American Chemical Society
Published on Web 08/15/2008

at nicotinic receptors.[4] Despite synthetic efforts of several groups including our own resulting in several total syntheses, the absolute stereochemistry so far has not been elucidated.[5] Interestingly, recent studies carried out by the Gallagher group showed that no nicotinic activity could be observed for the synthetic racemate of epiquinamide.[6] In this manuscript, we report a new enantioselective route to (+)-epiquinamide, including unambiguous assignment of the absolute configuration.

Scheme 1. Retrosynthesis

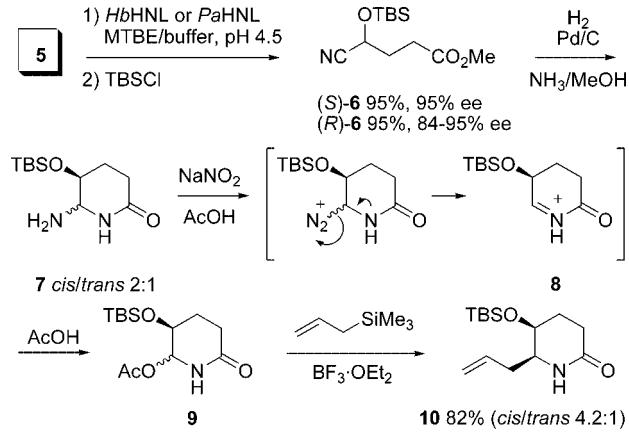


As depicted in Scheme 1, we envisaged obtaining epiquinamide from hydroxypiperidone derivative **2**. Piperidone **2** should be obtained via *N*-acyliminium ion **3** using nucleophilic allylation. We envisioned **3** to be derived from *N*,*N*-acetal **4**, which should be accessible from aldehyde **5** via chemoenzymatic enantioselective cyanohydrin formation and subsequent reductive ring closure.

Thus, the forward synthesis commenced with the readily prepared succinic semialdehyde **5**,[7] which was transformed into both enantiomeric forms of the corresponding cyanohydrins **6** using crude cell lysates from rubber tree- and almond-containing hydroxynitrile lyases. Hydroxynitrile lyases are designed by nature to convert cyanohydrins into the corresponding aldehydes and hydrogen cyanide, which are used by some plants as a defense system.

By using a two-phase system of water and methyl *tert*-butyl ether (MTBE), the equilibria can be directed to the side of the cyanohydrins.[8] In the case of semialdehyde **5**, the chemoenzymatic HCN addition provided, on a small scale after extensive optimization, both cyanohydrins in excellent yields and 95% ee using an (*S*)-selective HNL from *Hevea brasiliensis* (*Hb*HNL) and an (*R*)-selective HNL from *Prunus amygdalus* (*Pa*HNL, Scheme 2). We were also able to perform the enzymatic conversion with *Hb*HNL on a 25 g scale in the same ee and a similar 91% yield after subsequent TBS protection to give (*S*)-**6**. Scaling up using *Pa*HNL

Scheme 2. Formation of Both Enantiomers of Cyanohydrin **6**



appeared more difficult, eventually giving rise to a maximum ee of 84% and 95% yield of (*R*)-**6**, again after TBS protection. Fortunately, our synthetic strategy relied on the (*S*)-enantiomer to prepare the targeted natural product. Subsequent reductive amination of (*S*)-configured cyanohydrin **6** provided the corresponding *N*,*N*-acetal **7** as a 2:1 mixture of *cis*/*trans*-isomers in excellent yield using a recently published procedure.[9]

The next crucial step was the conversion of *N*,*N*-acetal **7** into a suitable *N*-acyliminium ion precursor, requiring conversion of the amine moiety into a leaving group employing, for example, protonation, acylation, or diazotation. The latter reaction proved to be the best. Sodium nitrite in neat acetic acid worked well. Acetic acid in this reaction acts both as the acid and as the nucleophile, attacking the transient *N*-acyliminium ion **8** to give the stable acetate **9**. This *N*,*O*-acetal appeared to be a suitable precursor for *N*-acyliminium ion chemistry under Lewis acid conditions. Reaction with allyltrimethylsilane as the nucleophile gave product **10** as a separable 4.2:1 mixture of *cis*/*trans*-isomers in 82% overall yield starting from cyanohydrin (*S*)-**6**.[10] The relative configuration of the *cis*-isomer was proven using X-ray crystallography (Figure 1).[11]

With the allyl-substituted piperidone **10** in hand, the stage was set for the formation of the bicyclic skeleton of epiquinamide. Allylation (NaH, allyl bromide) of the *cis*-isomer of **10** (Figure 1), followed by RCM and hydrogenation, provided **12** in a satisfactory yield of 81% (Scheme 3). TBAF-mediated deprotection of the TBS ether, followed by

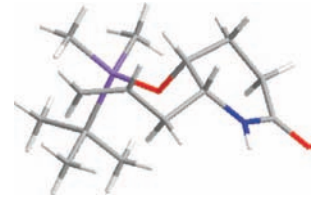


Figure 1. Crystal structure of compound *cis*-**10**.

(6) Kanakubo, A.; Gray, D.; Innocent, N.; Wonnacott, S.; Gallagher, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4648.
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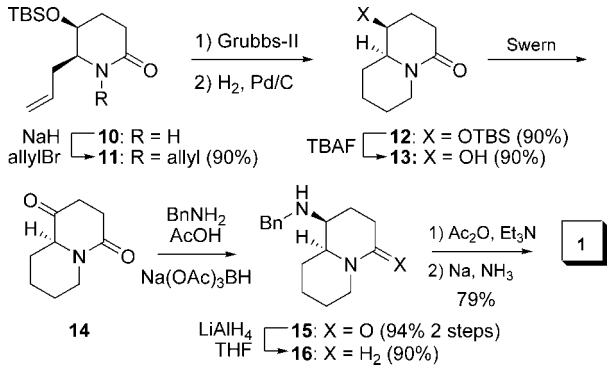
(8) Fechter, M. H.; Griengl, H. In *Enzyme catalysis in organic synthesis*; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, 2002; Vol *II*, pp 974−989, and references therein.
(9) Vink, M. K. S.; Schortinghuis, C. A.; Mackova-Zabelinskaja, A.; Fechter, M.; Pöchlauer, P.; Castelijns, A. M. C. F.; van Maarseveen, J. H.; Hiemstra, H.; Griengl, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2003**, *345*, 483.

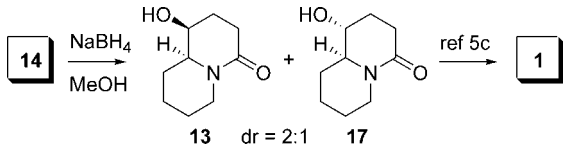
Scheme 3. Synthesis of Epiquinamide



Swern oxidation, gave the bicyclic ketone **14** in excellent overall yield. Conversion of the ketone function into the properly configured amine was initially attempted using reductive amination. Indeed, reductive amination with benzylamine provided the desired diastereoisomer **15** in a selective manner in 94% over two steps. However, presumably due to the acidic conditions of the reductive amination, the intermediate imine partially racemized—possibly via the corresponding enamide—to give **15** in only 70% ee. Conditions were varied to prevent racemization, but this appeared not possible without a large decrease in yield or diastereoselectivity. Nevertheless, the synthetic plan was continued by first reducing the lactam moiety using $LiAlH_4$ to cleanly afford diamine **16** in 90% yield. Next, the benzylic amine moiety was acetylated and debenzylated through dissolving metal reduction to afford (+)-epiquinamide **1** in 70% ee. Analytical data were in accordance with literature data.[5a]

To circumvent the racemization step, ketone **14** in an alternative approach was reduced with the small hydride donor sodium borohydride (Scheme 4). This indeed resulted

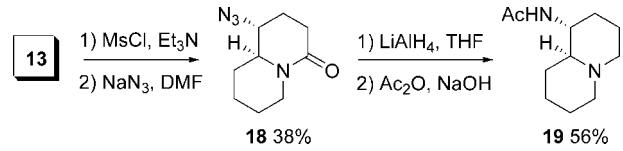
Scheme 4. Formal Synthesis of Epiquinamide



in the desired intermediate **17** without racemization but as the minor reaction product along with the undesired epimer **13** in a 1:2 ratio. Chromatographic separation of the two isomers thus represents a formal synthesis of the natural product since recent work has shown that epiquinamide can be prepared from **17** in four steps.[5c]

Furthermore, this route was used to prepare the epimer of epiquinamide (**19**) as depicted in Scheme 5. Mesylation of

Scheme 5. Synthesis of C(1)-Epiepiquinamide (**19**)



alcohol **13**, followed by azide substitution, provided **18** in a moderate 38% yield, caused by significant amounts of elimination product which could not be avoided by altering the conditions. Next, $LiAlH_4$ reduction followed by acetylation gave *epi*epiquinamide (**19**) in 56% yield.

Finally, racemic and synthetic enantiopure (+)-epiquinamide[5a] were subjected to chiral GC as was the natural compound showing that (+)-epiquinamide and the natural compound were identical.

In conclusion, a synthetic pathway for (+)-epiquinamide has been developed, involving chemoenzymatic enantioselective cyanohydrin formation using hydroxynitrile lyases and conversion of *N*,*N*-acetals into stable *N*-acyliminium ion precursors. Having synthesized epiquinamide and determined its absolute configuration, this pathway can be used for the synthesis of analogues with potentially useful biological activity, which is currently under investigation in our laboratory.

Acknowledgment. This research is performed as part of the IBOS Program (Integration of Biosynthesis & Organic Synthesis) of ACTS−NWO. C. van den Broek (DSM Pharma Chemicals) is kindly acknowledged for assistance with the large scale HNL experiments.

Supporting Information Available: Procedures, synthesis, and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For a similar example of an endocyclic *N*-acyliminium ion reaction, see: Huang, P.-Q.; Wei, B.-G.; Ruan, Y.-P. *Synlett* **2003**, 1663.

(11) Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-677971.