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Atropurpuran – Missing Biosynthetic Link Leading to the Hetidine and Arcutine C_{20}-Diterpenoid Alkaloids or an Oxidative Degradation Product?

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Abstract

A possible biosynthetic link between atropurpuran, the hetidine diterpenoid alkaloids and the alkaloid arcutine and congeners is proposed. The feasibility of aspects of this biosynthesis, especially key 1,2-rearrangements, have been examined computationally.

Keywords

Biosynthesis; diterpenoid alkaloids; hetidine; arcutines; oxidation

1. Introduction

Plants from the *Aconitum* genus have been used in traditional Chinese medicine for centuries. These plants produce a large variety of biologically interesting substances, including diterpenoid alkaloids. To date, over 1,200 diterpenoid alkaloid natural products divided into the C_{18}, C_{19}, and C_{20} classes have been isolated and characterized. In 2000 and 2001, Saidhhodzhaeva and Bassonova reported the isolation and characterization of two structurally unique alkaloids found in the leaves of *Aconitum arcuatum* Maxim., arcutine (**1a**) and arcutinine (**1b**, Figure 1).[1] Until the discovery of atropurpuran (**2**) in 2009 by the Wang group,[2] the arcutines (**1a** and **1b**) were the only known secondary metabolites that featured a tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]tridecane motif. Additionally, these alkaloids are the only diterpenoid alkaloids that possess a bond between C5 and C20 rather than the usual C10–C20 linkage (see hetidine core **3** for numbering). Even though it is not an alkaloid, the framework of atropurpuran (**2**) maps directly onto the arcutine skeleton. It therefore seems likely that atropurpuran is either a biosynthetic precursor to, or a metabolite of, the arcutines.

Wang and coworkers have proposed that atropurpuran may arise from hetidine-type precursor **4** (Scheme 1). [2] In their biosynthetic proposal, fragmentation of the C13–C14

bond of **4** would lead to di-aldehyde **5**. A retro-Diels-Alder reaction involving the loss of ethylene would yield cyclohexadienone **6**, which could then be engaged by hydroxide in an oxo-Michael-type addition. The resulting enolate (**7**) could then undergo a Diels-Alder reaction with ethylene to form a [2.2.2] bicycle (see enolate **8**). A dehydration to afford **9**, which was expected to undergo an intramolecular aldol reaction to arrive at compound **10**, was then proposed. From there, a series of redox events would afford the atropurpuran framework. Several aspects of this proposed biosynthesis seemed unlikely to us, which prompted us to revisit the biogenesis of these compounds and to propose alternative biosynthetic pathways, which are the subject of this Letter.

The biosynthesis of the diterpenoid alkaloids is believed to take place in two principal phases (Scheme 2).[3] Geranylgeranyl pyrophosphate (**GGPP**) is believed to undergo a polyene cyclization cascade to give *ent*-copalyl diphosphate (***ent*-CPP**). The exocyclic olefin in ***ent*-CPP** then undergoes annulation to arrive at **11**. *ent*-Atisir-16-ene **12** (an atisane type diterpene) ultimately results following a series of Wagner-Meerwein rearrangements involving non-classical carbocations and a 1,2-H shift.[4] The second phase of the biosynthesis is not well understood, but is believed to commence with the oxidation of **12** to give a di-aldehyde or a synthetic equivalent such as **13**. A double reductive amination with a nitrogen source[5] would form the piperidine moiety found in the atisine core (**14**). The hetidine core (**3**) can then arise by a Mannich reaction to install the final C–C bond.[6] The C_{20}-diterpenoid alkaloids (such as the atisines bearing the core (**4**) are widely accepted to serve as biosynthetic precursors to the C_{18}- and C_{19}-diterpenoid alkaloids.[7]

2. Results and Discussion

Atropurpuran (**2**) was isolated alongside a variety of C_{19}-diterpenoid alkaloids, which led us to propose that the C_{20}-precursors to the C_{19}-diterpenoid alkaloids might also give rise to atropurpuran. Due to their structural resemblance, we also suspect that the arcutines could arise from this pathway.[8] As a starting point in a potential biosynthesis picture, *ent*-atisir-16-ene (**12**) can be converted to **15** by C14–C20 bond formation following oxidation (Scheme 3). The alcohol group in **15** could be ionized to arrive at cationic intermediate **16**. This species could then undergo 1,2-acyl shift to form the [5.3.3.$0^{4,9}$.$0^{4,12}$]tridecane scaffold (**17**).[9] Elimination and subsequent hydroxylation would yield atropurpuran (**2**). Alternatively, cation **17** might be hydroxylated to give **18**. Reductive amination[5] and allylic oxygenation at this stage would then lead to the arcutines.

An alternative scenario involves the formation of the arcutines from a hetidine-type precursor such as **3** via a C–C bond migration. In Pathway A (Scheme 4), **3** is first hydroxylated at C5. The tertiary hydroxy group in **19** may be protonated, leading to the elimination of water as described above. The resulting carbocation (**20**) could then undergo a 1,2-alkyl shift to generate carbocation **21**. Hydration, followed by oxidation of the secondary amine, would give arcutinidine (**1c**). Alternatively, imine **22** (formed *via* Pathway B) could undergo a 1,2-C(sp^2) migration, to give arcutinidine (**1c**) directly. N-oxidation of arcutinidine to form nitrone **24** would yield hydroxylamine **25** upon hydrolysis. Loss of two equivalents of water and hydrolysis of the resulting imine would furnish atropurpuran (**2**).

These possible biosynthetic scenarios inspired us to examine the origin of these compounds by applying theoretical tools to assess the viability of several of the proposed transformations, particularly a 1,2-alkyl shift (**A**→**B**→**C**, Figure 2) and a 1,2-acyl shift (**16**→**D**→**17**, Figure 2) to form the arcutine/atropurpuran frameworks.

Computational calculations were carried out using the Gaussian09 REV C01 package[11] and the mPW1K[12] or the B3LYP[13] hybrid functionals in combination with the 6–31+G(d,p) basis set.[14] Analysis of **A**, a model cationic intermediate for **20**, found an associated transition state energy of +4.8 kcal mol^{-1} in the gas phase for its conversion to **C**. Modeling the same 1,2-shift in water yielded a barrier of +5.7 kcal mol^{-1}. Although this transformation is slightly endergonic, the overall process (**19**→**23**) is exergonic by −2.1 kcal mol^{-1}.[15] For the proposed 1,2-acyl shift (i.e., **16**→**17**), a barrier of +7.7 kcal mol^{-1} (**D**) was found in both environments (i.e., in the modeled gas and water phases). The transformation in water was found to be exergonic, whereas the same rearrangement in the gas phase was slightly endergonic (+1.3 and −2.4 kcal mol^{-1}, respectively).

3. Conclusion

In conclusion, we propose that atropurpuran and the arcutine family of molecules could arise from C_{20} diterpenoid alkaloid type precursors (such as the hetidine core) via skeletal rearrangements and oxidative degradation (in the case of atropurpuran) or from an earlier intermediate in the diterpenoid alkaloid biogenesis (such as ent-atisir-16-ene; for atropurpuran). Our computational analyses indicate that key 1,2-shifts associated with these processes likely proceed along reaction coordinates that avoid high-energy intermediates and transition states. These studies are only preliminary and a conclusion as to which scenario (i.e., formation of atropurpuran followed by reductive amination to form the arcutines or oxidative degradation of the arcutine alkaloids to yield atropurpuran) could not be reached simply by our current analysis. Should one of the biosynthetic possibilities that we propose be confirmed, it would serve to unite these interesting families of natural products with the rest of the C_{20} diterpenoid alkaloids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. a) Tashkhodzhaev B, Saidkhodzhaeva SA, Bessonova IA, Antipin MY. Chem Nat Compd. 2000; 36:79.b) Saidkhodzhaeva SA, Bessonova IA, Abdullaev ND. Chem Nat Compd. 2001; 37:466.
2. Tang P, Chen QH, Wang FP. Tetrahedron Letters. 2009; 50:460.
3. a) Chen K, Baran PS. Nature. 2009; 459:824. [PubMed: 19440196] b) Davis EM, Croteau R. Top Curr Chem. 2000; 209:53.c) Maimone TJ, Baran PS. Nature Chem Biol. 2007; 3:396. [PubMed: 17576427]

4. Christianson DW. Chem Rev. 2006; 106:3412. [PubMed: 16895335] For a computational analysis of diterpene biosynthetic pathways see: Hong YJ, Tantillo DJ. J Am Chem Soc. 2010; 132:5375. [PubMed: 20353180] Helv Chim Act. 2014; 97:1475.Tantillo DJ. Nat Prod Rep. 2011; 28:1035. (Review). [PubMed: 21541432]
5. Several nitrogen sources (e.g., methylamine, ethylamine, β-aminoethanol and *S*-adenosylmethionine) have been proposed as precursors to the nitrogen atom found in the diterpene alkaloids (see Ref. 6c, pp 87). However, to date, only L-serine has been identified as a nitrogen source, see Ref. 6b.
6. a) Peese, KM.; Gin, DY. Total Synthesis of Natural Products: At the Frontiers of Organic Chemistry. Li, JJ.; Corey, EJ., editors. Springer Science & Business Media; Heidelberg: 2013. b) Zhao PJ, Gao S, Fan LM, Nie JL, He HP, Zeng Y, Shen YM, Hao XJ. J Nat Prod. 2009; 72:645. [PubMed: 19275222] c) Wang, F-P.; Liang, X-T. The Alkaloids: Chemistry and Biology. Cordell, GA., editor. Vol. 59. Academic Press; 2002. p. 1
7. Wang, F-P.; Chen, Q-H. The Alkaloids: Chemistry and Biology. Cordell, GA., editor. Vol. 69. Academic Press; 2010. p. 1
8. Previously Wang and Liang classified the arcutines as a rearranged class (C-II′) of the hetidines or hetisines, see reference 6c.
9. The overall transformation could also occur in a dyotropic manner, see e.g., Davis RL, Leverett CA, Romo D, Tantillo DJ. J Org Chem. 2011; 76:7167. [PubMed: 21770451]
10. CYLview, 1.0b. Legault, C. Y: Université de Sherbrooke; 2009. (http://www.cylview.org)
11. Frisch, MJ.; Trucks, GW.; Schlegel, HB.; Scuseria, GE.; Robb, MA.; Cheeseman, JR.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, GA.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, HP.; Izmaylov, AF.; Bloino, J.; Zheng, G.; Sonnenberg, JL.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, JA., Jr; Peralta, JE.; Ogliaro, F.; Bearpark, M.; Heyd, JJ.; Brothers, E.; Kudin, KN.; Staroverov, VN.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, JC.; Iyengar, SS.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, JM.; Klene, M.; Knox, JE.; Cross, JB.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, RE.; Yazyev, O.; Austin, AJ.; Cammi, R.; Pomelli, C.; Ochterski, JW.; Martin, RL.; Morokuma, K.; Zakrzewski, VG.; Voth, GA.; Salvador, P.; Dannenberg, JJ.; Dapprich, S.; Daniels, AD.; Farkas, Ö.; Foresman, JB.; Ortiz, JV.; Cioslowski, J.; Fox, DJ. Gaussian 09, Revision C.01. Gaussian, Inc; Wallingford CT: 2009.
12. a) Lynch BJ, Fast PI, Harris M, Truhlar DG. J Phys Chem A. 2000; 104:4811.b) Lynch BJ, Truhlar DG. J Phys Chem A. 2001; 105:2936.
13. a) Becke AD. J Chem Phys. 1993; 98:5648.b) Lee C, Yang W, Parr RG. Phys Rev B. 1998; 37:785.c) Vosko SH, Wilk L, Nusair M. Can J Phys. 1980; 58:1200.
14. Ditchfield R, Hehre WJ, Pople JA. J Chem Phys. 1971; 54:724.Hehre WJ, Ditchfield R, Pople JA. J Chem Phys. 1972; 56:2257.
15. Data included in the Supporting Information.

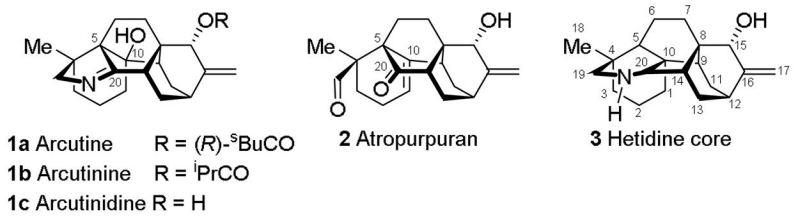


Figure 1.
The arcutines **1a**–**1c**, atropurpuran **2** and the hetidine core **3**.

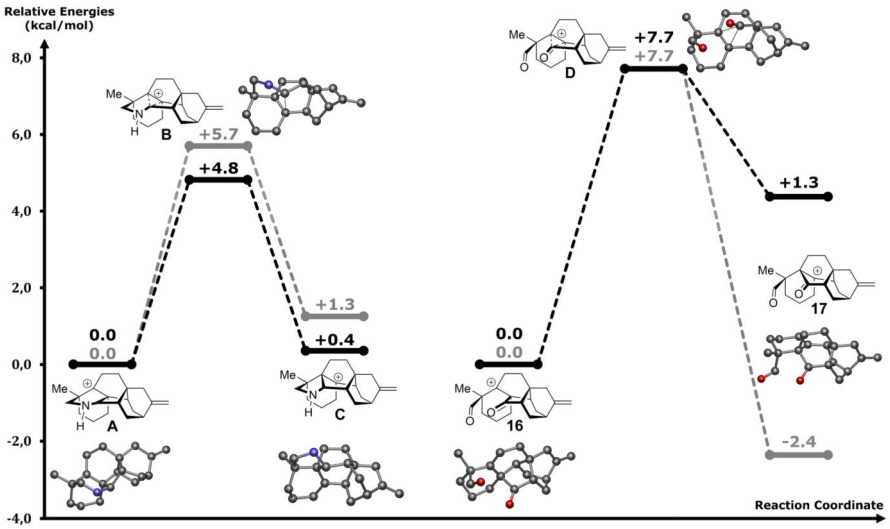
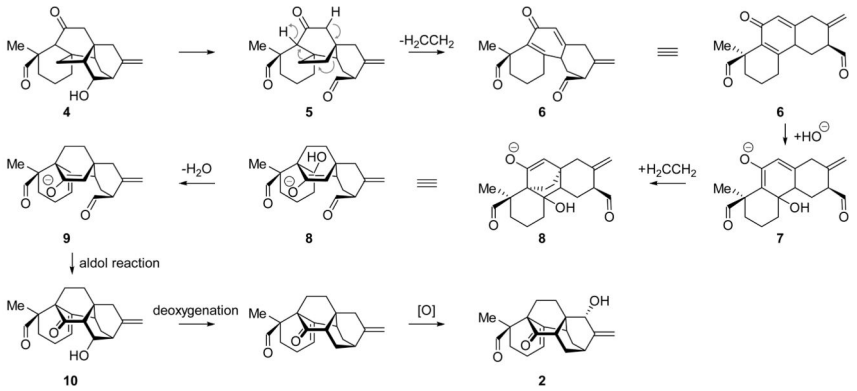


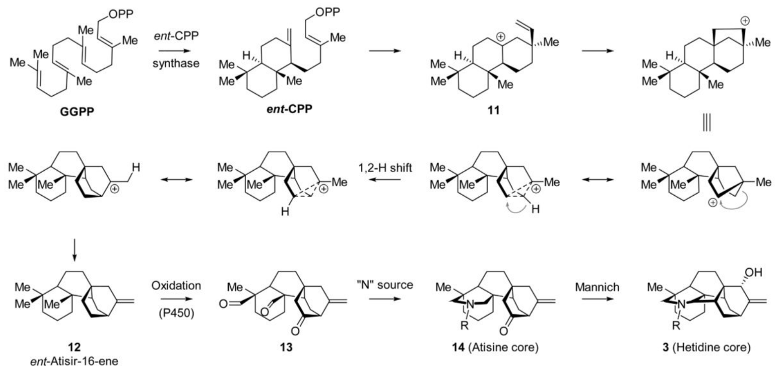
Figure 2.

Energy profile of the proposed 1,2-alkyl shift (left) and 1,2-acyl shift (right). Black numbers represent relative gas phase energies reported in kcal mol^{-1}, grey numbers are the corresponding energies in water. All energies include zero-point energy correction. All structures were visualized using CYLview.[10]



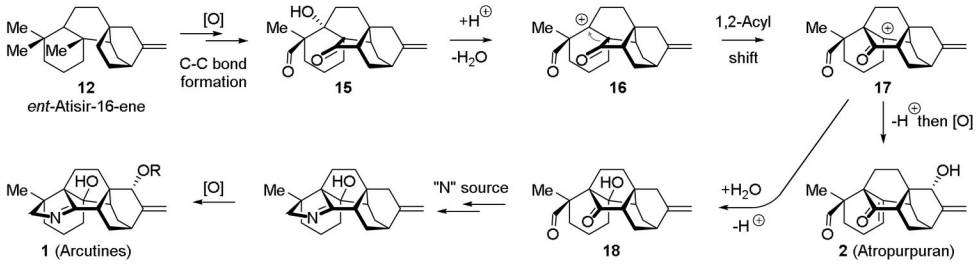
Scheme 1.

Proposed biosynthesis of atropurpuran by Wang and coworkers.[2]



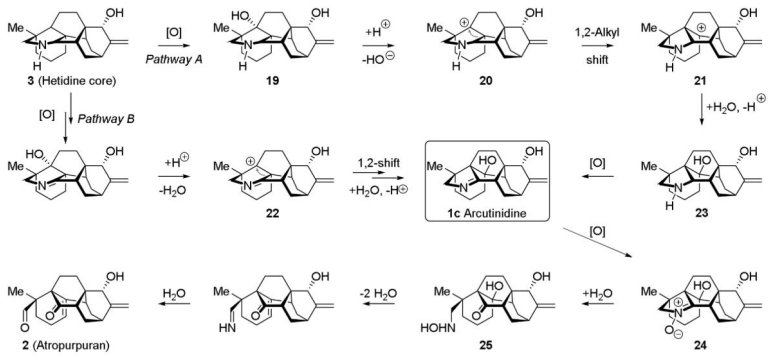
Scheme 2.

Biosynthesis of the hetidine-type C_{20}-diterpenoid alkaloids.



Scheme 3.

Possible biosynthetic transformation of **12** to atropurpuran and the arcutines.



Scheme 4.

Proposed biogenesis of the arcutines and atropurpuran from a hetidine-type precursor **3**.