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Biomimetic Synthesis of Elysiapyrones A and B

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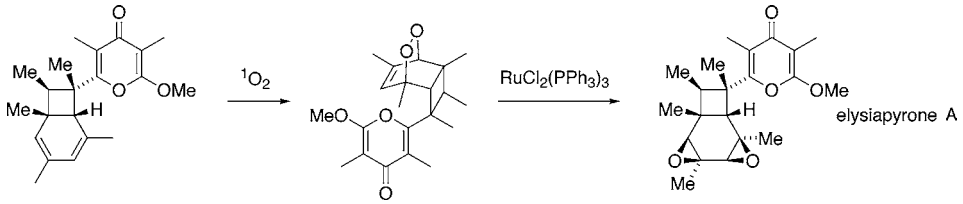
ABSTRACT



The total synthesis of bicyclo[4.2.0]octane natural products elysiapyrones A and B is described.

Until recently, natural products featuring a bicyclo[4.2.0]-octane or octadiene skeleton have been rarely reported. However, more than two decades after the identification and prediction of the first representatives of this class, endiandric acids D and E, respectively,[1] several compounds have surfaced in the literature that share their basic architecture and biosynthetic pattern. The unusual immunosuppressants SNF4435 C (**3**) and D (**4**) were isolated from *Streptomyces spectabilis*,[2] whereas the unnamed natural products **5** and **6**,[3] as well as elysiapyrones A (**7**) and B (**8**),[4] were found in the saccoglossan mollusks *Placobranchus ocellatus* and *Elysia diomedea*, respectively (Figure 1).

Biosynthetically, these natural products presumably stem from $8\pi-6\pi$ electrocyclization cascades involving (*Z*,*Z*)-tetraenes, as originally proposed by Black.[1a] This pathway has been synthetically corroborated for compounds **1**−**5**.[1b,3b,5] The bis-epoxide moiety found in the elysiapyrones was proposed to arise via isomerization of an *endo*-peroxide corresponding to **6**, which in turn stems from [4 + 2] cycloaddition of singlet oxygen to the cyclohexadiene portion of a bicyclo[4.2.0]octadiene.[4] Note that this simple sequence results in stereochemically intriguing compounds that feature a chiral center on each carbon of their bicyclic core.

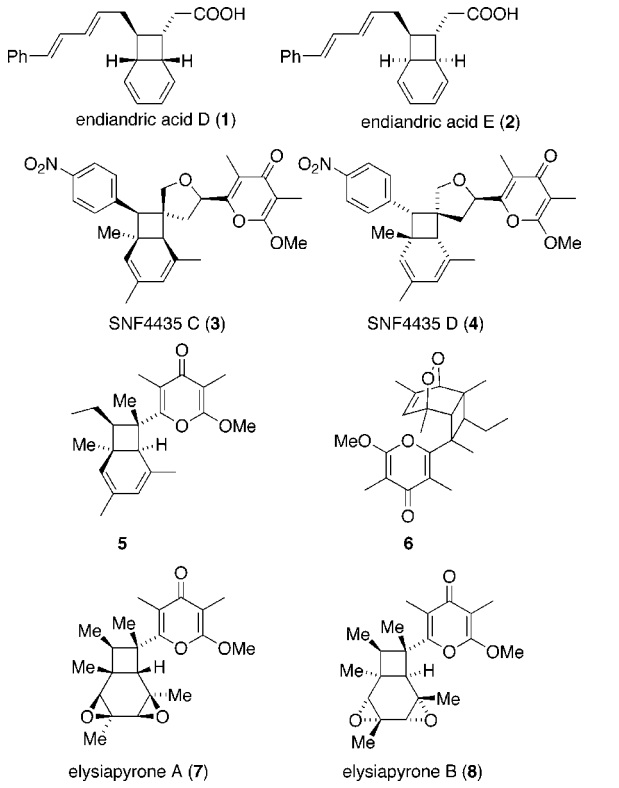


Figure 1. Bicyclo[4.2.0]octane (octadiene) natural products.

(1) (a) Banfield, J. E.; Black, D. St. C.; Johns, S. R.: Willing, R. I. *Aust. J. Chem.* **1982**, *35*, 2247 and references therein. (b) Nicolaou, K. C.; Sorensen. E. J. In *Classics in Total Synthesis*; VCH: Weinheim 1996; p 265 and references therein.

(2) (a) Kurosawa, K.; Takahashi, K.; Tsuda, E. *J. Antibiot.* **2001**, *54*, 541. (b) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548.

(3) (a) Manzo, E.; Ciavatta, M. L.; Gavagnin, M.; Mollo, E.; Wahidulla, S.; Cimino, G. *Tetrahedron Lett.* **2005**, *46*, 465. The correct structure of compound **5** was reassigned by total synthesis: (b) Miller, A. K.; Trauner. D. *Angew. Chem., Int. Ed.* **2005**, in press. We propose to call **5** and **6** ocellapyrones A and B respectively.

(4) Cueto, M.; D'Croz, L.; Maté, J. L.; San-Martín, A.; Darias, J. *Org. Lett.* **2005**, *7*, 415.

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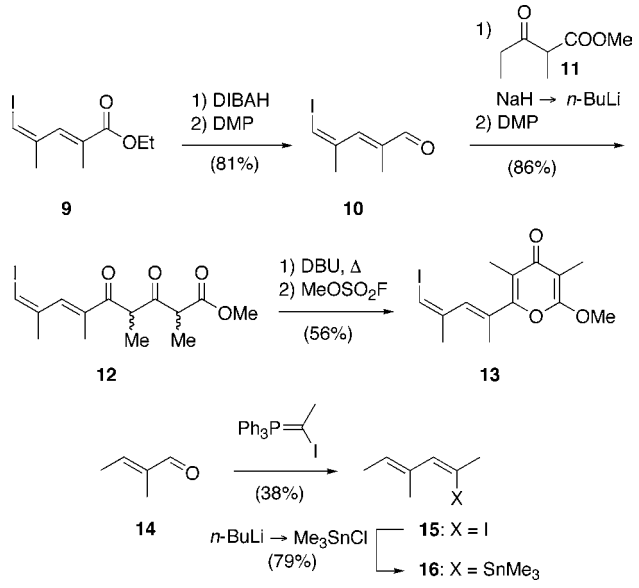
We now wish to present a short, biomimetic synthesis of racemic elysiapyrones A and B that follows along these lines. Our synthetic pathway starts with the known iododienoic ester **9**,[6] which was converted into dienal **10** using standard redox chemistry. Addition of the dianion of β-ketoester **11** followed by oxidation afforded diketo ester **12** as a mixture of stereoisomers, which was taken on without further purification. Base-mediated cyclocondensation followed by regioselective methylation under Beak's conditions[7] then afforded key building block **13** (Scheme 1).[8]

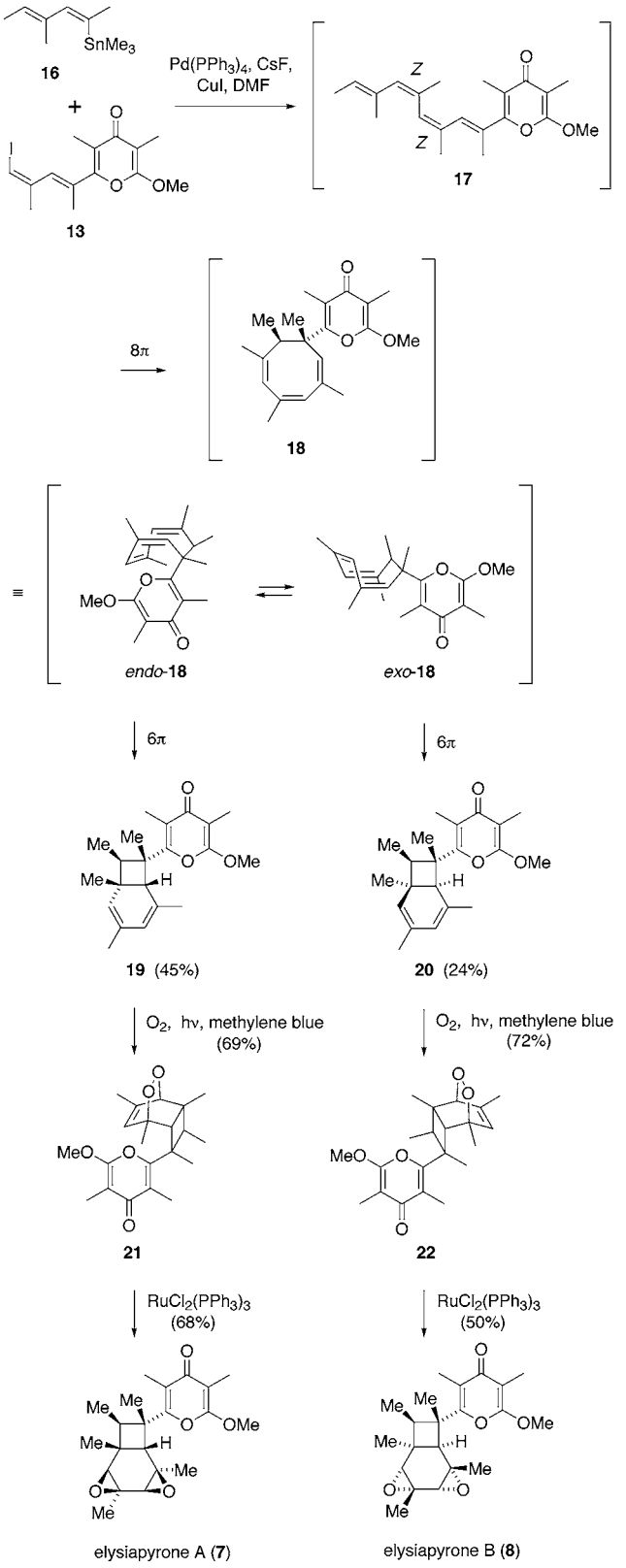
Scheme 1. Synthesis of Building Blocks **13** and **16**



The second half of the tetraene precursor was assembled by Stork−Zhao olefination of the commercially available aldehyde **14** followed by lithiation of the resulting sensitive (*Z*)-vinyl iodide **15** and interception of the vinyllithium intermediate with trimethyl tin chloride.[9] This afforded the stable (*Z*)-vinyltin compound **16** with retention of double-bond geometry.

Stille coupling[10] of **13** and **16** presumably gave tetraene **17**, which underwent in situ 8π electrocyclization (**17** → **18**), followed by 6π electrocyclization of the cyclooctatriene conformers *endo*-**18** and *exo*-**18**. The resulting diastereomeric bicyclo[4.2.0]octadienes **19** and **20** were formed in 45% and 24% yield, respectively, under these conditions. This kinetic preference for the thermodynamically presumably less stable

Scheme 2. Synthesis of Elysiapyrones A and B



endo-diastereomer has been noted in similar electrocyclization cascades.[3b,5b]

Bicyclo[4.2.0]octadienes **19** and **20** were taken on separately to the elysiapyrones. To this end, each isomer was

(5) (a) Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221. (b) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington; R. M.; Cowley, A. R. *Org. Lett.* **2002**, *4*, 3731. (c) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 641. (d) Parker, K. A.; Lim, J. H. *J. Am. Chem. Soc.* **2004**, *126*, 15968.

(6) Parker, K. A.; Lim, Y. H. *Org. Lett.* **2004**, *6*, 161.

(7) Beak, P.; Lee, J. K.; Mckinnie, B. G. *J. Org. Chem.* **1978**, *43*, 1367.

(8) Compound **13** has also been made by Baldwin et al. through a different route in the context of a synthesis of **5**. See ref 3b.

(9) Ashe, A. J., III; Lohr, L. L.; Al-Tawell, S. M. *Organometallics* **1991**, *10*, 2424.

(10) Mee, S. P. H.; Lee, V.; Baldwin, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132.

reacted with singlet oxygen to afford *endo*-peroxides **21** and **22**, respectively.[11] Although it has been suggested that the α-methoxy-γ-pyrone moiety itself could function as a photosensitizer,[12] we found it more effective to use methylene blue for this transformation. Finally, *endo*-peroxides **21** and **22** were isomerized using Noyori's ruthenium(II)-catalyzed method,[13] which cleanly afforded elysiapyrones A and B (Scheme 2). Our synthetic material proved to be identical in all respects with the natural products with the exception of their optical rotation.

In summary, we have achieved a short, biomimetic synthesis of two complex natural products featuring electrocyclizations and cycloadditions as well as a transition metal catalyzed isomerization of an *endo*-peroxide. Asymmetric approaches based on chiral palladium complexes or host−guest chemistry are under active investigation. The application of an analogous strategy to the synthesis of compounds **5** and **6** has been achieved and will be published elsewhere.[3b]

(11) Compound **22** was obtained under these conditions together with varying amounts (20−35%) of inseparable compound **21**. The reason for this contamination is under investigation.

(12) Zuldema, D. R.; Jones. P. B. *J. Nat. Prod.* **2005**, *68*, 481.

(13) Suzuki, M.; Ohtake, H.; Kameya, Y.; Hamanaka, N.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 5292.

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Supporting Information Available: Spectroscopic and analytical data for compounds **7**, **8**, **10**, **13**, **15**, **16**, and **19**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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