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A synthetic strategy to bridged 2,3,8-trioxabicyclo[3,3,1]nonane endoperoxides

Sandra Gemma [a,b], Sanil Kunjir [a,b], Margherita Brindisi [a,b], Ettore Novellino [a,c], Giuseppe Campiani [a,b,*], Stefania Butini [a,b]

[a] European Research Centre for Drug Discovery and Development (NatSynDrugs), University of Siena, via Aldo Moro 2, 53100 Siena, Italy
[b] Centro Interuniversitario di Ricerche sulla Malaria, Università di Torino, Torino, Italy
[c] Dipartimento di Chimica Farmaceutica e Tossicologica, University of Naples Federico II, via D. Montesano 49, 80131 Naples, Italy

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ABSTRACT

As a part of our work in the development of novel antimalarials, we were interested in elaborating an appropriate synthetic strategy for the preparation of endoperoxide-containing bridged bicyclic scaffolds. Through a TMSOTf-promoted dehydrative cyclization strategy we synthesized 2,3,8-trioxabicyclo [3,3,1]nonane endoperoxides. Alkyl substituents at C4 of the bicyclic scaffold could be readily introduced through exposure to Grignard reagents.

Introduction

Peroxide-based antimalarials such as artemisinin (**1**, Fig. 1) and its semisynthetic derivatives are the only highly effective therapy for the treatment of malaria caused by chloroquine-resistant *Plasmodium falciparum* strains. Although highly effective, artemisinins are also expensive, and this factor limits the wide distribution of these drugs to malaria endemic countries.[1,2] Since the discovery of artemisinin, research activities have been focused in developing more affordable endoperoxides characterized by the same highly effective mechanism of action of artemisinin (linked to the presence of the endoperoxide moiety) but endowed with simplified and more synthetically affordable chemical scaffolds.[3–9]

Several natural compounds have been isolated and are characterized by the presence of the endoperoxide ring system. Among them, dihydroplakortin (**2**)[10,11] and Yingzhaosu A (**3**)[12] show interesting antimalarial properties, and are characterized by an overall simpler scaffold with respect to artemisinin. As a part of our work in the design and synthesis of novel antimalarials,[13–18] we recently focused our research activities on the development of endoperoxides based on structural analogues of 9,10-dihydroplakortin, a natural product isolated from the Caribbean sponge *Plakortis simplex*. In particular, we described the total synthesis of dihydroplakortin and prepared 9,10-dihydroplakortin analogues with a simplified structure.[11,19]

More recently, we disclosed a novel class of bicyclic analogues of dihydroplakortin having a tetrahydrofuro[2,3-*c*][1,2]dioxane system (typified by **4**).[20] For the preparation of these analogues

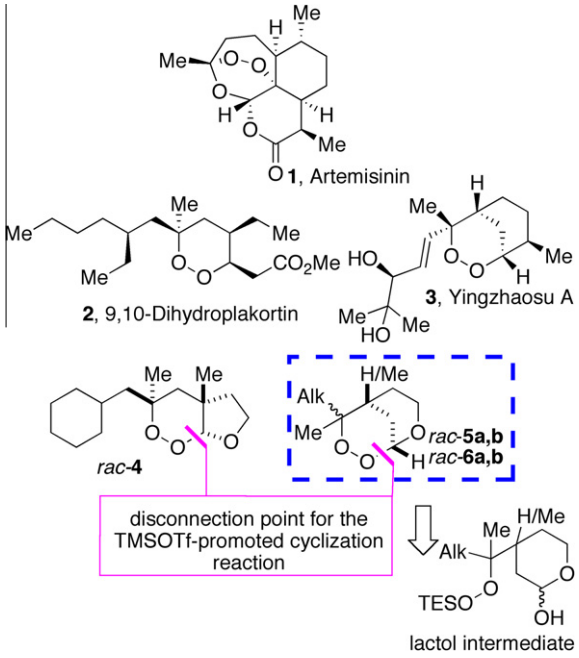

Figure 1. Reference and title compounds.

* Corresponding author. Tel.: +39 0577 234172; fax: +39 0577 234333.
E-mail address: campiani@unisi.it (G. Campiani).

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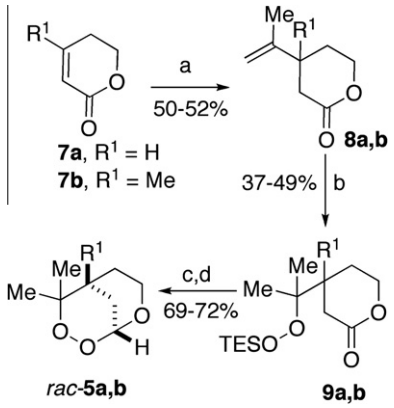
we developed a trimethylsilyl triflate (TMSOTf)-promoted dehydrative cyclization of lactols.

The natural compound Yingzhaosu A (**3**) presents a 2,3-dioxabicyclo[3,3,1]nonane scaffold that has been exploited for the synthesis of potent analogues (e.g., arteflene and ant its carvone-derived peroxyacetal analogues).[21–24] In order to explore the potential of our cyclization protocol and to synthesize novel endoperoxide-containing scaffolds, we decided to prepare the 2,3,8-trioxabicyclo[3,3,1]nonane peroxyacetals **5a**,**b** and **6a**,**b** shown in Figure 1. These derivatives combine the bridged endoperoxide ring of Yingzhaosu A with the cyclic peroxyacetal moiety of artemisinin. These endoperoxides could be synthesized exploiting our cyclization strategy, starting from the lactol intermediate shown in Figure 1. In particular, TMSOTf simultaneously promotes the deprotection of the peroxide moiety and the dehydrative cyclization.

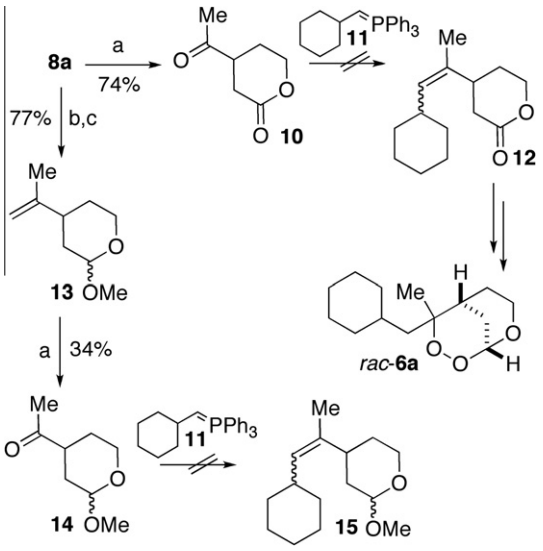
The synthesis of C4-dimethyl endoperoxides **5a**,**b** is described in Scheme 1. Pyranones **7a**,**b**[25,26] were prepared as described in the literature and reacted with isopropenylmagnesium bromide in the presence of copper(I) bromide to afford olefin intermediates **8a**,**b**.[27–29] Regioselective hydroperoxysilylation at the disubstituted olefin carbon of compounds **8a**,**b** was accomplished under an O_2 atmosphere using bis(2,2,6,6-tetramethylheptane-3,5-dienoate) Co(II) ($Co(thd)_2$) as the catalyst, in the presence of triethylsilane.[11,19,30] Subsequently, intermediates **9a**,**b** were subjected to a DIBAL-promoted reduction of the lactone carbonyl group. Exposure of the resulting lactol derivatives to TMSOTf at −78 °C for 5 min efficiently afforded the target compounds **5a**,**b**.[31]

In our previous series of bicyclic derivatives, the C3 aliphatic chain displayed a key role in modulating the antimalarial activity of the endoperoxides. Accordingly, we explored the possibility of introducing different alkyl chains at C4 of the bridged endoperoxide scaffold (compounds **6a**,**b**). The trisubstituted olefin **12** (Scheme 2) was a key intermediate for the synthesis of **6a**. As described in Scheme 2, the olefin moiety of **8a** was subjected to an ozonolysis reaction in order to obtain ketone **10**. In our original plan, we hypothesized that this versatile intermediate could be readily converted into a variety of trisubstituted olefins exploiting the classical Wittig olefination reaction conditions.

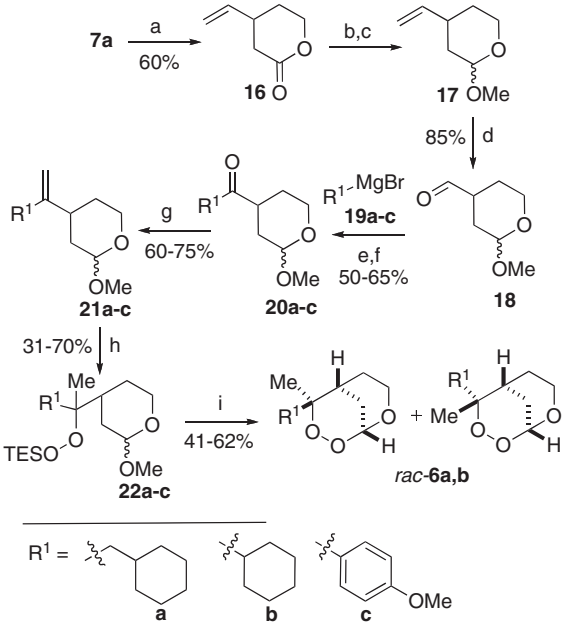
However, when ketone **10** was treated with the phosphorous ylide **11**, the expected olefin **12** was not isolated from the reaction mixture. The same results were obtained when the protected cyclic acetal **14** was subjected to the same olefination protocol. Intermediate **14** was in turn readily obtained from **8a** by reduction of the lactone and protection of the resulting lactol as the corresponding cyclic acetal **13**, followed by ozonolysis of the olefin.



Scheme 1. Synthesis of bicyclic endoperoxides *rac*-**5a**,**b**. Reagents and conditions: (a) isopropenylmagnesium bromide, CuI, THF, −78 °C, 3 h; (b) Et_3SiH, $Co(thd)_2$, O_2, DCE, *t*-BuOOH, 25 °C, 4 h; (c) DIBAL, DCM, −78 °C, 1.5 h; (d) TMSOTf, DCM, −78 °C, 5 min.



Scheme 2. Attempted syntheses of intermediate **12**. Reagents and conditions: (a) (i) O_3, DCM, −78 °C, 40 min, (ii) dimethylsulfide, −78 °C, 25 min; (b) DIBAL, DCM, −78 °C, 1.5 h; (c) *p*-TsOH, MeOH, 25 °C, 40 min.



Scheme 3. Synthesis of bicyclic endoperoxides *rac*-**6a**,**b**. Reagents and conditions: (a) vinylmagnesium bromide, CuI, THF, −78 °C, 3 h; (b) DIBAL, DCM, −78 °C, 1.5 h; (c) *p*-TsOH, MeOH, 25 °C, 40 min; (d) (i) O_3, DCM, −78 °C, 40 min, (ii) PPh_3, −78 °C, 25 min; (e) **19a–c**, THF, reflux, 1 h; (f) Dess–Martin periodinane, DCM, 25 °C, 30 min; (g) PPh_3CH_3Br, *n*-BuLi, THF, −40 °C, 1 h, 25 °C, 2 h; (h) Et_3SiH, $Co(thd)_2$ (for **21a**,**b**) or $Co(acac)_2$ (for **21c**), O_2, *t*-BuOOH, 25 °C, 4 h; (i) TMSOTf, −78 °C, 5 min.

Due to synthetic constraints in obtaining intermediate **12**, probably due to an inherent low reactivity of the cyclohexylemethylene Wittig reagent, we decided to modify the synthetic route as described in Scheme 3. Indeed, exploiting the regiochemistry of the hydroperoxysilylation reaction, in which the peroxide moiety is selectively placed at the most substituted olefin carbon, the target intermediate **22a** could also be obtained from gem-disubstituted olefins as the substrates for the hydroperoxysilylation reaction.

Following the above-described strategy, pyranone **7a** was converted into the vinyl derivative **16** by reaction with vinyl magnesium bromide in the presence of copper(I) iodide. The lactone moiety of **16** was then protected as the corresponding cyclic acetal

through a two-step procedure involving DIBAL-promoted reduction of the carbonyl group followed by acetalization in methanol. Ozonolysis of the terminal olefin furnished aldehyde **18**, which was then reacted with different Grignard reagents **19a–c** to furnish the corresponding secondary alcohols. These latter compounds were oxidized to the corresponding ketones **20a–c** using Dess–Martin periodinane in DCM. At this point of the synthetic pathway, olefination of the carbonyl group with methylphosphorane afforded the desired olefins **21a–c**, bearing cyclohexylmethyl-, cyclohexyl-, or 4-methoxyphenyl-substituents, respectively.

Compounds **21a–c** were smoothly converted into the corresponding hydroperoxysilylated intermediates **22a–c**. For compounds **21a**,**b** $Co(thd)_2$ was used as the catalyst. On the contrary, the higher reactivity of **21c** toward the oxidation reaction resulted into the decomposition of the starting material. Starting from **21c**, the less reactive $Co(acac)_2$ catalyst smoothly furnished intermediate **22c**. Finally, TMSOTf-promoted cyclization of **22a**,**b** afforded the expected bridged endoperoxides **6a**,**b**[32] as inseparable mixture of diastereoisomers. However, under the same reaction conditions, extensive decomposition of **21c** was observed leading to a complex mixture of by-products that could not be characterized. Several attempts to perform the cyclization reaction under milder conditions, or prior fluoride-promoted deprotection of the silyl group, were unsuccessful.

In conclusion, we successfully applied the TMSOTf-promoted cyclization reaction of silylperoxide-containing lactols for the synthesis of 2,3,8-trioxa[3,3,1]nonanes, an unprecedently described scaffold for developing new antimalarials. Moreover, we developed a versatile synthetic strategy for introducing different alkyl substituents at the C4 that takes advantage of readily available Grignard reagents. This synthetic methodology will pave the way to the exploration of the structure–activity relationships study of a novel class of bridged peroxyacetals.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.075.

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31. *4,4-Dimethyl-2,3,8-trioxabicyclo[3.3.1]nonane* (***5a***): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (s, 1H), 4.81–4.67 (m, 1H), 3.97–3.84 (m, 1H), 2.31–2.21 (m, 1H), 2.13–1.90 (m, 2H), 1.80–1.68 (m, 2H), 1.47 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.9, 81.5, 64.6, 31.2, 29.0, 27.2, 25.2, 24.4; MS (ESI) *m/z* 181 $(M+Na)^+$; HRMS ($C_8H_{14}NaO_3$) 181.0835, found: 181.0830. *4,4,5-Trimethyl-2,3,8-trioxabicyclo[3.3.1]nonane* (***5b***): ^{1}H NMR ($CDCl_3$) δ 5.19 (t, *J* = 2.2 Hz, 1H), 4.79–4.64 (m, 1H), 4.00–3.90 (m, 1H), 2.09 (dt, *J* = 13.0, 3.0 Hz, 1H), 2.04–1.92 (m, 1H), 1.77–7.57 (m, 1H), 1.45 (d, *J* = 2.1 Hz, 1H), 1.42 (s, 3H), 1.16 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.3, 85.1, 65.9, 35.6, 35.1, 31.2, 25.3, 21.5, 21.0. MS (ESI) *m/z* 195 $(M+Na)^+$. HRMS ($C_9H_{16}NaO_3$) 195.0992, found: 195.0986.
32. *4-Cyclohexylmethyl-4-methyl-2,3,8-trioxabicyclo[3.3.1]nonane* (***6a***): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16–5.13 (m, 2H), 4.83–4.68 (m, 2H), 3.98–3.86 (m, 2H), 2.35–2.19 (m, 2H), 2.12–1.95 (m, 4H), 1.94–1.56 (m, 16H), 1.99 (s, 3H), 1.33–1.13 (m, 9H), 1.12–0.79 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.1, 95.9, 84.1, 83.9, 64.7, 64.6, 45.0, 43.0, 35.5, 35.4, 35.0, 34.5, 34.0, 33.3, 30.7, 29.9, 29.8, 28.9, 27,3, 27.1, 27.6, 26.5, 26.4, 26.3, 22.5, 21.2; MS (ESI) *m/z* 263 $(M+Na)^+$. HRMS ($C_{14}H_{24}NaO_3$) 263.1618, found: 263.1612. *4-Cyclohexyl-4-methyl-2,3,8-trioxabicyclo[3.3.1]nonane* (***6b***): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (s, 2H), 4.87–4.71 (m, 2H), 4.04–3.87 (m, 2H), 2.38 -2.20 (m, 2H), 2.20–1.91 (m, 6H), 1.92–1.64 (m, 10H), 1.64–1.45 (m, 3H), 1.36 (s, 3H), 1.34–1.04 (m, 10H), 1.05–0.85 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.0, 95.8, 85.6, 85.0, 65.1, 64.6, 43.3, 40.0, 29.0, 28.5, 28.2, 28.1, 27.3, 27.2, 27.1, 26.9, 26.8, 26.7, 26.6, 26.4, 26.3, 26.1, 17.5, 16.2; MS (ESI) *m/z* 249 $(M+Na)^+$; HRMS ($C_{13}H_{22}NaO_3$) 249.1461, found: 249.1465.