Pergamon

Tetrahedron Letters 43 (2002) 2127–2131

TETRAHEDRON LETTERS

# Hetero-Diels–Alder reaction of halogenated quinones with a polygodial-derived azadiene

Mauricio A. Cuellar, Luz K. Alegría, Yolanda A. Prieto, Manuel J. Cortés,* Ricardo A. Tapia* and Marcelo D. Preite*

*Departamento de Química Orgánica, Facultad de Química, Pontificia Universidad Católica de Chile, Vicuña Mackenna 4860, Casilla 306, Correo 22, Santiago, Chile*

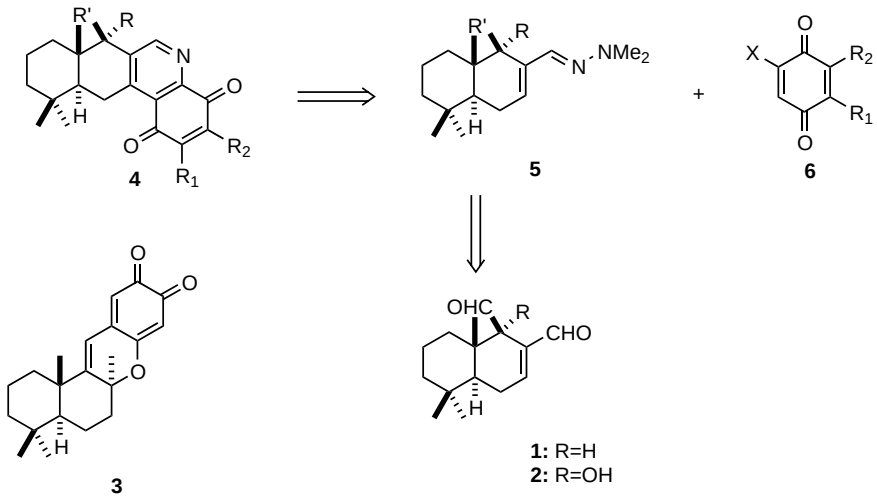
Received 31 January 2002; accepted 1 February 2002

**Abstract**—The reaction between polygodial dimethylhydrazone and haloquinones under an air atmosphere is described. The terpene moiety undergoes a degradative oxidation to an 11-norsequiterpene ketone containing a quinolinequinone skeleton.


## 1. Introduction

It is a well known fact that unsaturated drimanic dicarbonyl compounds such as polygodial (**1**) and warburganal (**2**) show remarkable biological activities, associated with the ability of the unsaturated dicarbonyl system to form a pyrrole ring by addition of the amino group of aminoacids.[1] Several other substances containing sesquiterpene drimane and quinone moieties also show important bioactivities, like several cytotoxic and anti-tuberculosis compounds structurally related to puupehedione (**3**).[2,3]

As part of a search for new synthetic biologically active heterocyclic quinones, we were interested in synthesizing compounds combining a drimane skeleton with an azaquinone, as in general structure **4** (Scheme 1). Compound **4** can be disconnected from a retrosynthetic point of view into two fragments: **5**, an azadiene related to the naturally occurring sesquiterpene polygodial (**1**),




**Scheme 1.**

*Keywords*: hetero-Diels–Alder reaction; haloquinones; quinolinequinone synthesis.
* Corresponding authors. Tel.: +56-2-686-4436; fax: +56-2-686-4744; e-mail: mpreite@puc.cl

0040-4039/02/$ - see front matter 
PII: S0040-4039(02)00246-0

and **6**, a simple 2-haloquinone,[4] via a Diels–Alder reaction as the key step.[5]

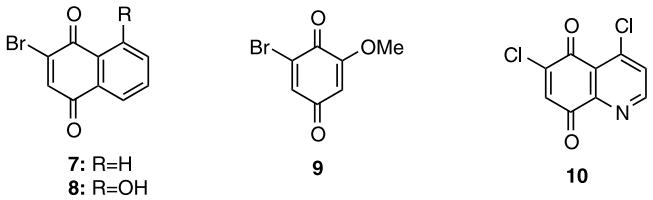
The first example of a hetero-Diels–Alder reaction of a 1-aza-1,3-diene was reported in 1982 by Ghosez et al.[6] The hetero-Diels–Alder reaction of α,β-unsaturated *N*,*N*-dimethylhydrazones and quinones has been successfully applied to the synthesis of azaanthraquinones.[7,8] However, there were no previous examples of a complex asymmetric azadiene like **5**. A useful precedent was the use of α-haloquinones as dienophiles, that couple efficiently and regioselectively with 1-azadienes.[8] The tacit aromatization step was reported to occur spontaneously after elimination of hydrogen halides and dimethylamine.[6]

Herein we report the first example of a drimane-derived *N*,*N*-dimethylhydrazone used as a diene in hetero-Diels–Alder cycloaddition reactions.

## 2. Results and discussion

Treatment of **1**,[1] obtained from the hexanes extract of the bark of South American '*Winter's bark*' tree (*Drymis winteri Forst*.) with *N*,*N*-dimethylhydrazine in $CCl_4$ in the presence of anhydrous $MgSO_4$ at 0°C afforded hydrazone **5** (89% yield), as a white solid.[9] In a preliminary assay, a Diels–Alder reaction of **5** and benzoquinone was attempted. Unfortunately, we were unable to get any reaction product even under forcing conditions, conducting to decomposition of the starting materials. As a way to increase the reactivity of the system, it was decided to try the same reaction with some simple 2-haloquinones.[8]

2-Bromonaphthoquinone (**7**) and 3-bromojuglone (**8**) were prepared according to a reported procedure.[10,11] 2-Bromo-6-*O*-methyl-1,4-benzoquinone (**9**) was prepared from vanillin, by a bromination,[12] followed by a Bayer–Villiger oxidation, and in situ oxidation to the quinone.[13] 4,6-Dichloroquinoline-5,8-dione (**10**) was prepared following a previously reported procedure[14] (Scheme 2).

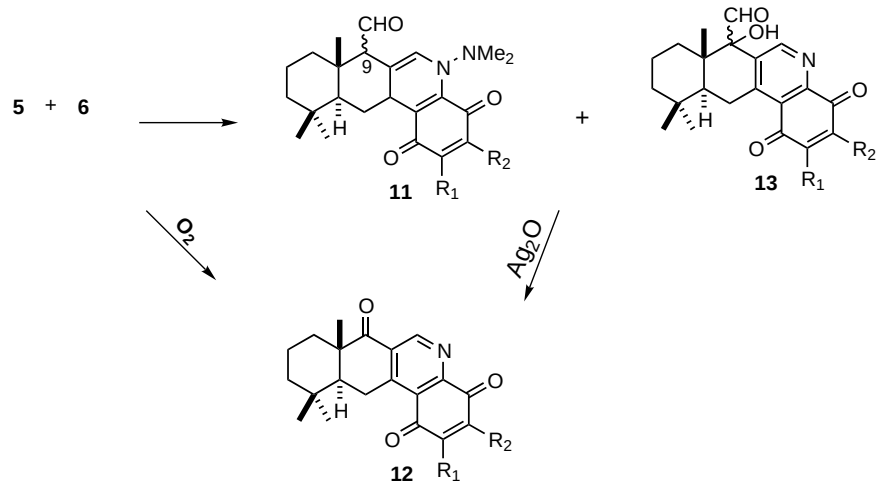



**Scheme 2.**

The regiochemistry of the final products of type **12** was assumed to be as shown under the basis of the previous observation done by Fillion et al.,[5] that the nucleophilic end of azadienes of type **5** attacks exclusively the unbrominated carbon atom of bromoquinones. Furthermore, bidimensional NMR studies of compounds **12** revealed the existence of long-range $^{1}H$–$^{13}C$ HMBC couplings between H-6 and C-5′ or C-9′, confirming the proposed structure and allowing a full assignment of the NMR spectra.[19]

When azadiene **5** was reacted with haloquinones **7**–**10** (Scheme 3) in the presence of $NaHCO_3$ and under nitrogen, an unseparable mixture of the aldehydes **11**, epimeric at C-9, and the decarbonylated product **12**, was obtained. In order to accelerate the formation of **12**, and for characterization purposes, this crude mixture was submitted to oxidation with $Ag_2O$, thus affording an 11-norsesquiterpene-quinone of type **12**.[15,16] To our delight, when the reactions were performed under air, in open vessels, solid products of type **12** were directly obtained. The results of these reactions are summarized in Table 1.[19]

The observation of a carbonyl loss in the presence of air in a pyridine derivative like **12** is, to the best of our knowledge, unprecedented. Nevertheless, there was a previous report on a similar carbon loss suffered by an α-hydroxy-α,α-diarylacetaldehyde during its treatment with silica gel in ethyl acetate,[17] suggesting the easy decarbonylation of an α-hydroxycarbonyl derivative,




**Scheme 3.**

**Table 1.** Reaction conditions

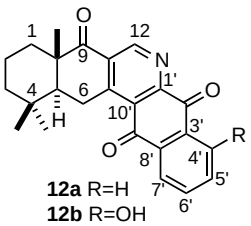
| Entry | Starting material | Solvent, conditions, atmosphere, time | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **7** | $CH_3CN$, reflux, air, 24 h | **12a** | 62.4 |
| 2[a] | **7** | $CH_3CN$, reflux, $N_2$, 24 h | **11a** | 37.0 |
| 3 | **8** | $CH_3CN$, reflux, air, 24 h | **12b** | 67.6 |
| 4 | **9** | $CH_3CN$, room temperature, air, 21 h | **12c** | 29.0 |
| 5 | **10** | $CH_3CN$, room temperature, air, 120 h | **12d** | 50.0 |

[a] This reaction was conducted in a previously evacuated flask, flushed several times with anhydrous nitrogen.

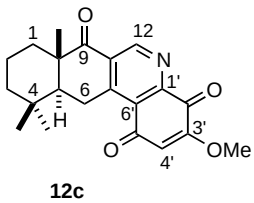
**Table 2.** PM3 orbital coefficients of HOMO for diene **5** and LUMO for quinones **7–10**

| Compound | Energy | N atom | C-X | CH | C-7[b] |
|---|---|---|---|---|---|
| **5**[a] | −8.803390 | −0.29930 | – | – | 0.36852 |
| **7** | −1.703507 | – | C-2: −0.35890 | C-3: 0.37096 | – |
| **8** | −1.620576 | – | C-2: −0.34120 | C-3: 0.35102 | – |
| **9** | −1.778994 | – | C-2: 0.36843 | C-3: −0.40312 | – |
| **10** | −1.871787 | – | C-6: 0.31715 | C-7: −0.32763 | – |

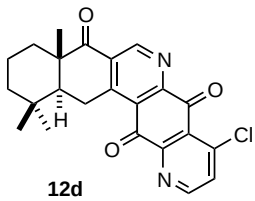
[a] Corresponds to the HOMO.
[b] Normal terpene numbering.




**12a** R=H
**12b** R=OH




**12c**




**12d**

and a detailed mechanism had been proposed for the air oxidation of phenylmalonate enolates.[18] Based on these precedents, for this reaction we propose the series of events depicted in Scheme 3. Starting with adduct **11**, an elimination of dimethylamine and of hydrogen halide and an oxidation of C-9, benzylic and α- to a carbonyl group, would produce hydroxyaldehyde **13** that, after decarbonylation, should give ketone **12**.[16,19]

The observed regioselectivity of the cycloaddition reaction is in good agreement with the previous observation that the major cycloadduct arises from the interaction of frontier orbitals with the largest orbital coefficients on the diene and dienophile, except for the case of reaction with quinone **8**, where the opposite selectivity was observed.[15] To verify this hypothesis, semiempirical calculations were performed at PM3 level,[20] using the software package Spartan®.[21] The calculation results are summarized in Table 2. A PM3 calculation on diene **5** shows that the larger orbital coefficient is located on C-7 (normal terpene numbering). In the case of quinone **8**, the semiempirical calculation puts a large orbital coefficient on C-3, the bromine-bearing atom. However, in this case, it was shown that a reversal in selectivity occurs,[15] and product **12b** is formed. For bromoquinone **9**, the PM3 calculations result in a large orbital coefficient located on C-3, i.e. the non-halogen-bearing carbon atom, leading to product **12c**. Finally, chloroquinone **10** has the larger orbital coefficient on C-7, the non-chlorinated atom, and forms **12d** on reaction with diene **5**.

## 3. Conclusions

In summary, we have described the first synthesis of a drimane-derived azadiene, and its Diels–Alder reactions with haloquinones to afford regioselectively 11-norsesquiterpene ketones in a fused quinolinequinone skeleton. We found very convenient to run the reactions in an air atmosphere, so allowing the aromatization and carbonyl loss, and providing solid products of type **12**. PM3 calculations are a useful tool to predict the regioselectivity of the reactions, which were determined by a full assignment of the NMR spectra, by the use of 2D NMR techniques.

## Acknowledgements

The authors thank FONDECYT-Fondo Nacional de Desarrollo Científico y Tecnológico (Grants No 8980003, 2010096, 2990104 and 2990098) for financial support. M.A.C., L.K.A. and Y.A.P. thank CONICYT (Consejo Nacional de Investigaciones Científicas y Tecnológicas) and DIPUC (Dirección de Investigaciones de la Pontificia Universidad Católica de Chile), for their fellowships.

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9. Mp 67–68°C (hexane); $[\alpha]_D^{18}$ −163.2° ($c=4.84$, $CHCl_3$); IR (KBr) 2723, 1715, 1640, 1576 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 0.89 (s, 3H, C-4-αMe), 0.93 (s, 3H, C-10-Me), 0.97 (s, 3H, C-4-βMe), 1.17–1.31 (m, 3H), 1.35–1.52 (m, 3H), 1.79–1.86 (m, 1H, H-1β), 2.05–2.26 (m, 2H, H-6), 2.74 (s, 6H, NMe), 2.75 (d: $J=5.1$ Hz, 1H, H-9), 6.05–6.10 (m, 1H, H-7), 6.95 (s, 1H, H-12), 9.45 (d: $J=5.1$ Hz, H-11); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 15.20 (q, C-10-Me), 18.14 (t, C-2), 22.17 (q, C-4-βMe), 24.06 (t, C-6), 33.11 (s, C-4), 33.31 (q, C-4-αMe), 36.89 (s, C-10), 39.62 (t, C-1), 42.03 (t, C-3), 42.64 (2 5 q, NMe), 49.38 (d, C-5), 61.82 (d, C-9), 131.55 (d, C-7), 132.53 (s, C-8), 135.15 (d, C-12), 203.09 (d, C-11). Elemental analysis: found: C, 73.97; H, 10.70; N, 10.09% ($C_{17}H_{28}N_2O$ requires: C, 73.87; H, 10.21; N, 10.13%).
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16. We detected a trace amount of a compound we assigned as the 9-hydroxyaldehydes **13a**, under the base of its $^1H$ NMR spectrum, together with the mixture of epimeric aldehydes at C-9 **11a**. Compound **11a**: a 2:1 mixture of epimers at C-9; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 0.98 (s, 3H, Me, major), 1.04 (s, 3H, Me, minor), 1.06 (s, 3H, Me, minor), 1.10 (s, 3H, Me, minor), 1.13 (s, 6H, 2×Me, major), 3.17 (dd, $J=12.2$ and 20.4 Hz, H-6β, major), 3.18 (overlapping dd, H-6β, minor), 3.45 (d: $J=3.5$ Hz, H-9, major), 3.55 (overlapping dd, H-6α, minor), 3.84 (dd, $J=5.3$ and 20.4 Hz, H-6α, major), 7.79–7.86 (m, 2H, H-5′ and H-6′), 8.22–8.38 (m, 2H, H-4′ and H-7′), 8.53 (s, H-12, minor), 9.89 (d, $J=3.5$ Hz, H-11, major), 9.82 (d, $J=3.7$ Hz, H-11, minor). Compound **13a**: a 2:1 mixture of epimers at C-9; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.06 (s, 3H, Me, minor), 1.10 (s, 3H, Me, major), 1.15 (s, 3H, Me, minor), 1.21 (s, 3H, Me, minor), 1.23 (s, 3H, Me, major), 2.03 (dd, $J=4.8$ and 13.4 Hz, H-5, major), 3.20 (dd, $J=12.2$ and 20.1 Hz, H-6β, major), 3.30 (dd, $J=12.6$ and 20.2 Hz, H-6β, minor), 3.71–3.92 (m, 1H, H-6α), 4.33 (disappears with $D_2O$, broad s, 1H, OH), 7.81–7.89 (m, 2H, H-5′ and H-6′), 8.25–8.40 (m, 2H, H-4′ and H-7′), 8.40 (s, H-12, major), 9.54 (s, 1H, H-11, minor), 10.02 (s, 1H, H-11, major).
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19. Compound **12a**: brown solid: mp 251.2–251.5°C; $[\alpha]_D^{15}$ −28.21° ($c=3.19$, $CHCl_3$); IR (KBr) 1775, 1695, 1683, 1592, 1556 $cm^{-1}$; $^1HNMR$ ($CDCl_3$, 200 MHz) $\delta$ 1.07 (s, 3H, C-4-αMe), 1.16 (s, 3H, C-10-Me), 1.19 (s, 3H, C-4-βMe), 1.53–1.76 (m, 6H), 2.01 (m, 1H, H-1β), 3.36 (dd: $J=12.3$, 20.3 Hz, 1H, H-6β), 3.91 (dd: $J=3.9$, 20.3 Hz, 1H, H-6α), 7.82–7.87 (m, 2H, H-5′ and H-6′), 8.25–8.37 (m, 2H, H-4′ and H-7′), 9.51 (s, 1H, H-12); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 16.67 (q, C-10-Me), 17.89 (t, C-2), 22.38 (q, C-4-βMe), 26.90 (t, C-6), 32.40 (q, C-4-αMe), 33.10 (t, C-1), 34.24 (s, C-4), 41.63 (t, C-3), 44.96 (s, C-10), 47.37 (d, C-5), 127.33 (d, C-4′), 127.57 (d, C-7′), 128.09 (s, C-10′), 129.37 (s, C-8), 132.45 (s, C-3′), 133.97 (s, C-8′), 134.49 (d, C-6′), 134.87 (d, C-5′), 151.51 (s, C-1′), 154.16 (d, C-12), 155.60 (s, C-7), 181.36 (s, C-9′), 184.70 (s, C-2′), 201.73 (s, C-9); microanalysis: C, 77.10; H, 6.28; N, 3.79% ($C_{24}H_{23}NO_3$ requires: C, 77.19; H, 6.21; N, 3.75%). Compound **12b**: orange solid: mp 273–274°C; IR (KBr) 3412 (br), 1703, 1675, 1640, 1566, 1552 $cm^{-1}$; $^1HNMR$ ($CDCl_3$, 200 MHz) $\delta$ 1.07 (s, 3H, C-4-αMe), 1.16 (s, 3H, C-10-Me), 1.19 (s, 3H, C-4-βMe), 1.54–1.76 (m, 6H), 1.99 (m, 1H, H-1β), 3.34 (dd: $J=12.2$, 20.3 Hz, 1H, H-6β), 3.89 (dd: $J=3.9$, 20.3 Hz, 1H, H-6α), 7.35 (dd: $J=1.74$, 7.83 Hz, 1H, H-7′), 7.70–7.83 (m, 2H, H-5′ and H-6′), 9.51 (s, 1H, H-12), 12.31 (s, 1H, C-4′-OH); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 16.65 (q, C-10-Me), 17.87 (t, C-2), 22.36 (q, C-4-βMe), 26.91 (t, C-6), 32.38 (q, C-4-αMe), 33.08 (t, C-1), 34.24 (s, C-4), 41.62 (t, C-3), 44.97 (s, C-10), 47.32 (d, C-5), 115.73 (s, C-3′), 119.80 (d, C-5′), 124.54 (d, C-7′), 128.40 (s, C-10′), 129.62 (s, C-8), 133.86 (s, C-8′), 137.59 (d, C-6′), 151.99 (s, C-1′), 154.18 (d, C-12), 155.69 (s, C-7), 183.88 (s, C-9′), 186.08 (s, C-2′), 201.60 (s, C-9); microanalysis: C, 73.31; H, 6.11; N, 3.58% ($C_{24}H_{23}NO_4$ requires: C, 73.02; H, 5.95; N, 3.60%). Compound **12c**: yellow solid: mp 196–197°C; IR (KBr) 1700, 1655, 1625, 1070 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.04 (s, 3H, C-4-αMe), 1.12 (s, 3H, C-10-Me),

1.15 (s, 3H, C-4-βMe), 1.20–1.80 (m, 6H), 2.01 (m, 1H, H-1β), 3.21 (dd: $J=12.3$, 20.2 Hz, 1H, H-6β), 3.84 (dd: $J=3.7$, 20.2 Hz, 1H, H-6α), 3.95 (s, 3H, OMe), 6.23 (s, 1H, H-4′), 9.43 (s, 1H, H-12); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 16.60 (q, C-10-Me), 17.88 (t, C-2), 22.26 (q, C-4-βMe), 26.21 (t, C-6), 32.42 (q, C-4-αMe), 33.08 (t, C-1), 34.24 (s, C-4), 41.62 (t, C-3), 44.98 (s, C-10), 47.33 (d, C-5), 56.70 (q, OMe), 111.80 (d, C-4′), 126.14 (s, C-6′), 129.50 (s, C-8), 149.39 (s, C-1′), 153.48 (d, C-12), 154.49 (s, C-7′), 159.5 (s, C-4′), 178.02 (s, C-2′), 185.82 (s, C-5′), 201.60 (s, C-9); microanalysis: C, 71.15; H, 6.50; N, 3.84% ($C_{21}H_{23}NO_4$ requires: C, 71.37; H, 6.56; N, 3.84%). Compound **12d**: yellow solid: mp 239–240°C; IR (KBr) 1690, 1280 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.05 (s, 3H, C-4-αMe), 1.17 (s, 3H, C-10-Me), 1.18 (s, 3H, C-4-βMe), 1.20–1.80 (m, 6H), 2.01 (m, 1H, H-1β), 3.38 (dd: $J=12.0$, 20.4 Hz, 1H, H-6β), 3.87 (dd: $J=3.9$, 20.4 Hz, 1H, H-6α), 7.79 (d: $J=5.2$ Hz, 1H, H-5′), 8.95 (d: $J=5.2$ Hz, 1H, H-6′), 9.55 (s, 1H, H-12); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 16.65 (q, C-10-Me), 17.87 (t, C-2), 22.32 (q, C-4-βMe), 26.81 (t, C-6), 32.30 (q, C-4-αMe), 33.10 (t, C-1), 34.28 (s, C-4), 41.62 (t, C-3), 45.02 (s, C-10), 47.39 (d, C-5), 126.78 (s, C-10′), 127.20 (s, C-3′), 129.51 (s, C-8), 130.90 (d, C-5′), 145.89 (s, C-8′), 151.09 (s, C-4′), 151.48 (s, C-1′), 154.30 (d, C-12), 154.7 (d, C-6′), 155.7 (s. C-7), 179.50 (s, C-2′), 182.08 (s, C-9′), 201.40 (s, C-9); microanalysis: C, 67.61; H, 5.06; N, 6.88% ($C_{23}H_{21}N_2O_3Cl$ requires: C, 67.56; H, 5.18; N, 6.85%).

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