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Semisynthesis of Macrocarpal C and Analogues by Selective Dehydration of Macrocarpal A or B

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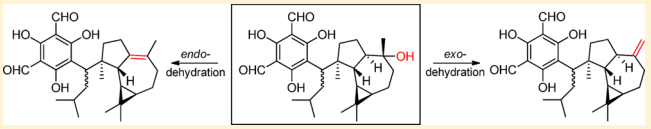
Supporting Information

ABSTRACT: Macrocarpals A and C are structurally related compounds that have been extracted from different *Eucalyptus* species. Although macrocarpal C is of biological interest, its isolation in pure form is difficult to achieve. We report herein an efficient method for the semisynthesis of macrocarpal C by selective *exo*-dehydration of another member of the macrocarpal family, macrocarpal A. We also report the semisynthesis of three new macrocarpal structures derived from either macrocarpal A or B.



Macrocarpals are "mixed" polyketide−diterpenoid naturally occurring compounds that have been isolated from plants of the *Eucalyptus* genus.[1] Macrocarpals possess an unusual skeleton that can be subdivided in two domains: a left-hand domain comprising a phloroglucinol dialdehyde moiety (common to all macrocarpals) and a right-hand terpenoid domain. Members of the macrocarpal family mainly differ by the stereochemistry of the C-1′ isobutyl side chain and by the presence or absence of a tertiary C-7 hydroxy group, which is replaced, in some cases, by an *exo*-double bond. Several macrocarpals have been extracted from *Eucalyptus* species (Figure 1) since the first isolation of macrocarpal A (**1a**) in 1990 by Aida, Hori, Ohashi, and co-workers.[2] The structure of **1a** was unambiguously assigned by X-ray crystallography. A couple of years later, two groups simultaneously reported the isolation and characterization of other macrocarpals, namely, macrocarpals B, C, D, E, F, and G.[3,4] Macrocarpals H, I, and J were also reported, but their terpenoid-like domain differs from that of macrocarpals investigated here.[5] While the structure of macrocarpal B (**1b**) was elucidated by single-crystal X-ray diffraction, that of the other macrocarpals were assigned using multidimensional NMR techniques. However, in the two independent reports mentioned above, NMR analyses were performed in different deuterated solvents, which rendered direct structure comparison difficult to achieve. In particular, confusion emerged[6] in the case of macrocarpals G[3] and C,[4] to which similar planar structures were attributed using 2D NMR analysis in methanol-d_4 and pyridine-d_5, respectively. However, in 1997, the picture became clearer with the completion of the first total synthesis of macrocarpal C. Indeed, the stereocontrolled synthesis of macrocarpal C[7,8] afforded a synthetic sample that exhibited spectroscopic data identical to those of natural macrocarpal C but surprisingly also to those of macrocarpal G. Hence, macrocarpals G and C share the same structure, **2a**.

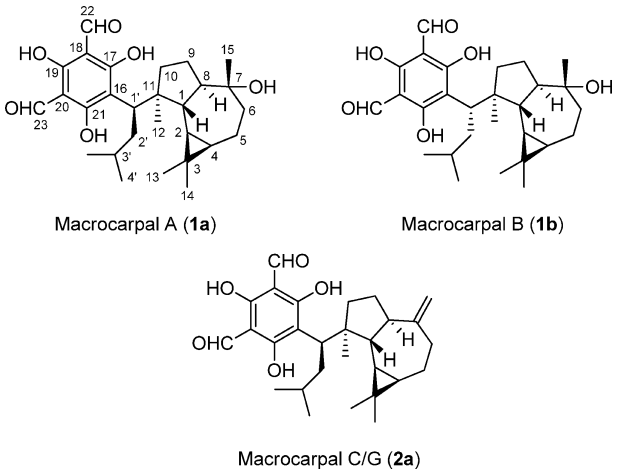


Figure 1. Examples of macrocarpal structures.

Macrocarpal C exhibits several interesting biological properties that are either common to other macrocarpals, e.g., antibacterial and antiviral activities, or specific to **2a**, e.g., anorectic effect.[9] A major limitation in the general utilization of **2a** in biological evaluations is related to its arduous isolation from the plant. On the contrary, **1a** can be readily crystallized from a methanolic extract. As **1a** and **2a** are structurally related, it is conceivable that regioselective dehydration of the tertiary alcohol moiety of **1a** could provide straightforward access to **2a**. We thus report here our approach for the selective dehydration of **1a** into **2a** (Scheme 1, path a). We also describe the semisynthesis of novel macrocapal structures derived from **1a** and **1b** by selective dehydration of the C-7 hydroxy group to afford either the *exo*- (**2**) or *endo*-dehydrated (**3** and/or **4**) macrocarpal structures (Scheme 1, paths a and b, respectively).

While various methods are reported for the dehydration of tertiary alcohols, regioselectivity of the process remains a

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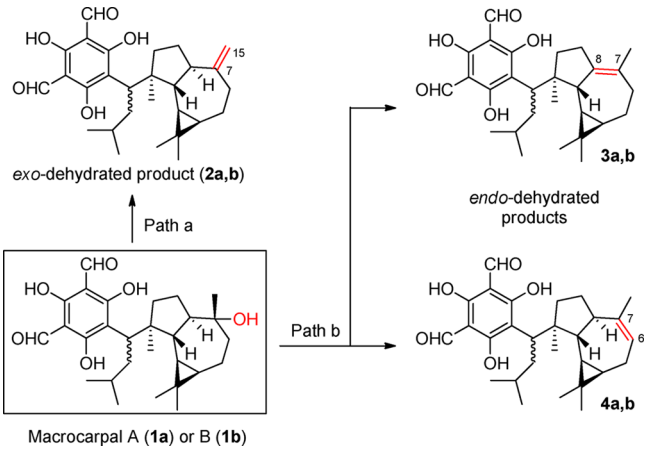
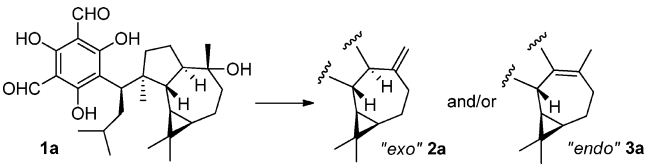
Scheme 1. Possible Dehydration Pathways of Macrocarpals



challenge. The *exo*-dehydration of macrocarpal A (**1a**) was nevertheless investigated, and some elimination conditions were screened. The use of thionyl chloride in combination with a base, e.g., pyridine, at different temperatures afforded a mixture of *endo*- (**3a**) and *exo*-dehydrated (**2a**) products (Table 1). The influence of low temperature on the regioselectivity of

Table 1. Conditions Investigated for the Selective *exo*-Dehydration of Macrocarpal A



entry	conditions	products *exo*/*endo*	yield of **2a**
1	$SOCl_2$, pyr, −50 °C, THF		no reaction
2	$SOCl_2$, pyr, −15 °C, THF	0.8:1	26%
3	$SOCl_2$, pyr, rt, THF	1:1	19%
4	$SOCl_2$, pyr, Δ, THF	2:1	27%
5	Martin's sulfurane, rt, CH_2Cl_2	1:1	37%
6	T3P, rt, THF		no reaction
7[a]	T3P, Δ, THF	9:1	41%
8	T3P, DTBPyr, Δ, THF	95:5	87%

[a]The reaction was stopped at ca. 50% conversion.

the process was studied and was found to have little impact on the product distribution. The reaction did not occur at −50 °C (Table 1, entry 1), but afforded a nearly stoichiometric mixture of the two alkenes (*exo*/*endo*) when increasing the temperature to −15 °C (entry 2). The latter observation also applies for the reaction at room temperature (entry 3). Better results were obtained by reacting **1a** with $SOCl_2$ in refluxing THF (entry 4), as a 2:1 ratio in favor of the expected *exo*-dehydrated product **2a** was obtained. However, under harsher conditions, some unidentified degradation products were detected. Notably the isomeric $\Delta^{6,7}$ *endo*-olefin **4a** could not be detected. The most substituted and hence thermodynamically more stable $\Delta^{7,8}$ *endo*-olefin **3a** resulted from H-8 elimination. The use of Martin's sulfurane[10] afforded the $\Delta^{7,15}$ and $\Delta^{7,8}$ isomers in equal amounts (entry 5). We finally turned our attention to the use of propylphosphonic anhydride (T3P), a reagent that was initially developed as a peptide coupling agent[11] (Figure 2).

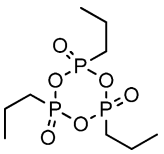


Figure 2. Structure of propylphosphonic anhydride (T3P).

While at room temperature no reaction occurred (entry 6), macrocarpal C (**2a**) was cleanly obtained as a major product (9:1 ratio) by regioselective *exo*-dehydration of macrocarpal A (**1a**) in refluxing THF. Indeed, pure **2a** was recovered in 41% yield after 2.5 h of reaction time (entry 7). The reaction was quenched at ca. 50% conversion (implying the recovery of ca. 50% of **1a**) because of the slow isomerization of the $\Delta^{7,15}$ *exo*-olefinic bond of compound **2a** into the $\Delta^{7,8}$ *endo*-double bond of compound **3a**. This isomerization process toward the most substituted *endo*-double bond was ascribed to the *in situ* formation of propylphosphonic acid that likely catalyzed the *exo* to *endo* migration of the olefinic bond. To minimize this rearrangement, the reaction was carried out in the presence of a base, e.g., pyridine, but side-products and a lower conversion were observed due to the addition of pyridine onto T3P. To avoid this side-reaction, we used the more hindered 2,5-di-*tert*-butylpyridine (DTBpyr), which was found to be efficient as mild base. Near quantitative conversion of **1a** into **2a** was indeed observed upon using DTBpyr with the formation of only minute amounts of the *endo*-dehydrated product **3a** (95:5, *exo*/*endo*). Macrocarpal C (**2a**) was isolated pure in 87% yield (entry 8).

As the above process was found to be quite efficient for the regioselective *exo*-dehydratation of macrocarpal A, the T3P-mediated process was also applied to macrocarpal B (**1b**), a C-1′ epimer of **1a**. Accordingly, when **1b** was reacted with T3P under the above conditions (heating in THF in the presence of DTBPyr), a novel macrocarpal structure, **2b**, was produced by selective *exo*-dehydration of the tertiary C-7 hydroxy group of **1b**. Compound **2b**, which has no literature precedent, was obtained pure in 89% yield. Again, when no base was used, slow isomerization of **2b** into **3b** was observed.

With the latter observation in mind, we conceived that novel macrocarpal structures, incorporating a $\Delta^{7,8}$ *endo*-olefinic moiety, could be accessed by *in situ* T3P-dehydration/isomerization. Accordingly, the reaction of macrocarpal A (**1a**) with T3P in refluxing THF led to an increase in the formation of the *endo*-isomer **3a**. Although the proportion of **3a** was >50% after 6 h of reflux in THF, some *exo*-product **2a** remained unaffected. Extended reaction time did not improve the product distribution but led to some degradation. Nevertheless, we found that the target transformation could be directly catalyzed by a strong acid instead of the *in situ* produced propylphosphinic acid. Macrocarpals A and B were hence reacted with sulfuric acid in substoichiometric amounts in THF for 1 h to provide, after the usual workup, hitherto unknown macrocarpal structures **3a** and **3b**, respectively, which were isolated in high yields: 90% from **1a** and 78% from **1b**. The latter incorporated an olefinic group whose $\Delta^{7,8}$ *endo*-nature was confirmed by 2D NMR experiments. This result is in agreement with the formation of the thermodynamically favored most substituted alkene as predicted by Zaitsev's rule.

In summary, we reported here the semisynthesis of macrocarpal C (**2a**) from macrocarpal A (**1a**). The process involved the selective T3P-mediated *exo*-dehydration of **1a**,

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which was also applied to macrocarpal B (**1b**). Reaction conditions were further adjusted to reverse the selectivity of the dehydration process and permit access to macrocarpal analogues bearing a $\Delta^{7,8}$ *endo*-double bond. Three hitherto unknown semisynthetic derivatives of macrocarpals, i.e., compounds **2b**, **3a**, and **3b**, were hence synthesized.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were determined using the sodium D line (589 nm) on a Perkin-Elmer 341 polarimeter. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts (δ) are expressed in ppm, and coupling constant (J) in hertz. Chemicals were purchased from Aldrich. Reactions were carried out using dry solvents. THF was distilled from sodium/benzophenone. Flash chromatography was carried out on Kieselgel 60 (230−240 mesh, Merck), and analytical TLC was performed on Merck precoated silica gel (60 F254); visualization was done with UV and/or heating with a solution of 5−7% phosphomolybdic acid in EtOH. HRMS spectra were recorded at "Service de Spectrométrie de Masse de l'Institut de Chimie des Substances Naturelles" in Gif-sur-Yvette (France).

General Procedure for *exo*-Dehydration of 1a or 1b. Under N_2, macrocarpal (**1a** or **1b**, 100 mg, 0.212 mmol, 1 equiv) was dissolved in anhydrous THF (10 mL) before T3P (1 mL of a 50% solution in EtOAc, 8 equiv) and DTBPyr (380 μL, 8 equiv) were added. The reaction mixture was heated at reflux for 6 h. It was then quenched with 1 M HCl (8 mL), and Et_2O (8 mL) was added. The organic phase was collected, and the aqueous layer was extracted with Et_2O (2 × 8 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified over silica (CH_2Cl_2/HOAc, 99.9:0.1 → 97:3) to give **2a** (from **1a**, 87%) or **2b** (from **1b**, 89%).

Compound 2a (macrocarpal C): $[\alpha]^{20}_D$ −25.8 (*c* 0.1, EtOH); IR (neat) ν_{max} 3204, 2952, 2867, 1627, 1446, 1307, 1185 cm^{-1}; ^{1}H NMR (methanol-d_4, 400 MHz) δ 0.62−0.72 (2H, m, H-4 and H-2), 0.78 (3H, d, J = 6.2 Hz, H-4′), 0.80 (3H, d, J = 6.2 Hz, H-4′), 0.81 (3H, s, H-12), 0.95 (1H, m, H-5), 1.01 (3H, s, H-14), 1.09 (3H, s, H-13), 1.18−1.23 (2H, m, H-3′ and H-2′), 1.30−1.43 (2H, m, H-10 and H-1), 1.67 (1H, m, H-9), 1.79 (1H, m, H-9), 1.96−2.08 (2H, m, H-6 and H-5), 2.22−2.47 (4H, m, H-8, H-6, H-10 and H-2′), 3.40 (1H, dd, J = 3.6 Hz, 12.8 Hz, H-1′), 4.64 (1H, s, H-15), 4.70 (1H, s, H-15), 10.11 (1H, s, H-22), 10.12 (1H, s, H-23); ^{13}C NMR (methanol-d_4, 100 MHz): δ 17.4, 21.0, 22.4, 23.9, 24.9, 26.8, 28.2, 28.5, 28.6, 29.3, 29.5, 36.0, 37.4, 38.7, 40.5, 50.6, 51.7, 52.5, 106.1, 106.1, 106.2, 111.3, 156.5, 168.7, 170.4, 170.9, 192.9, 193.1; negative HRESMS m/z 453.2623 (calcd for $C_{28}H_{37}O_5$, 453.2641 [M − H]$^-$).

Compound 2b: $[\alpha]^{20}_D$ +9.8 (*c* 0.1, EtOH); IR (neat) ν_{max} 3423, 2951, 2864, 1632, 1446, 1305, 1179 cm^{-1}; ^{1}H NMR (methanol-d_4, 400 MHz) δ 0.62−0.83 (5H, m, H-4, H-2 and H-4′),0.85 (3H, d, J = 6.5 Hz, H-4′), 1.00 (1H, m, H-5), 1.10−1.25 (11H, m, H-13, H-14, H-10, H-12, and H-3′), 1.27−1.40 (2H, m, H-1 and H-2′), 1.55 (1H, m, H-9), 1.63 (1H, m, H-10), 1.83 (1H, m, H-9), 1.96 (1H, m, H-6), 2.04 (1H, m, H-5), 2.38 (3H, m, H-8, H-6 and H-2′), 3.33 (1H, m, H-1′), 4.62 (1H, s, H-15), 4.69 (1H, s, H-15), 10.11 (1H, s, H-22), 10.12 (1H, s, H-23); ^{13}C NMR (methanol-d_4, 100 MHz) δ 17.5, 19.8, 20.7, 21.6, 24.8, 27.1, 27.3, 28.0, 28.1, 29.4, 31.7, 36.5, 40.6, 41.1, 42.7, 51.0, 54.8, 56.4, 105.6, 106.0, 106.1, 111.5, 157.0, 168.5, 170.4, 171.0, 193.1, 193.3; negative HRESMS m/z 453.2619 (calcd for $C_{28}H_{37}O_5$, 453.2641 [M − H]$^-$).

General Procedure for *endo*-Dehydration of 1a or 1b. Under N_2, macrocarpal (**1a** or **1b**, 50 mg, 0.106 mmol, 1 equiv) was dissolved in anhydrous THF (4 mL), and three drops of concentrated H_2SO_4 were added. After stirring for 1 h at room temperature, H_2O (5 mL) and Et_2O (5 mL) were added. The aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified over silica (CH_2Cl_2/HOAc, 99.9:0.1 → 99:1) to afford either **3a** (*endo*-A) (from **1a**, 90%) or **3b** (*endo*-B) (from **1b**, 78%).

Compound 3a: $[\alpha]^{20}_D$ −20.5 (*c* 0.06, EtOH); IR (neat) ν_{max} 2924, 1622, 1454, 1376, 1308, 1185 cm^{-1}; ^{1}H NMR (methanol-d_4, 400 MHz) δ 0.55 (1H, m, H-4), 0.68−0.76 (4H, m, H-12 and H-2), 0.81 (3H, d, J = 5.9 Hz, H-4′), 0.82 (3H, d, J = 5.8 Hz, H-4′), 1.05 (3H, s, H-13), 1.06 (3H, s, H-14), 1.10−1.22 (2H, m, H-2′ and H-3′), 1.41−1.50 (2H, m, H-10 and H-5), 1.52 (3H, s, H-15), 1.72 (1H, m, H-5), 1.85 (1H, m, H-10), 2.10−2.31 (4H, m, H-6 and H-9), 2.34 (1H, m, H-2′), 2.51 (1H, brs, H-1), 3.50 (1H, dd, J = 5.1 Hz, 14.6 Hz, H-1′), 10.11 (1H, s, H-22), 10.12 (1H, s, H-23); ^{13}C NMR (methanol-d_4, 100 MHz) δ 16.8, 20.0, 21.9, 22.2, 22.3, 24.2, 24.9, 27.4, 28.3, 29.1, 30.3, 31.5, 35.3, 35.7, 36.9, 37.2, 45.8, 49.7, 106.0, 106.1, 111.2, 126.7, 138.4, 168.6, 170.3, 171.0, 192.9, 193.1; negative HRESMS m/z 453.2637 (calcd for $C_{28}H_{37}O_5$, 453.2641 [M − H]$^-$).

Compound 3b: $[\alpha]^{20}_D$ +47.1 (*c* 0.1, EtOH); IR (neat) ν_{max} 2924, 1623, 1452, 1376, 1308, 1184 cm^{-1}; ^{1}H NMR (methanol-d_4, 400 MHz) δ 0.56 (1H, m, H-4), 0.76 0.84 (4H, m, H-2 and H-4′), 0.86 (3H, d, J = 6.4 Hz, H-4′), 1.05 (3H, s, H-12), 1.06 (3H, s, H-13), 1.07 (1H, m, H-10), 1.17 (3H, s, H-14), 1.22 (1H, m, H-3′), 1.33−1.42 (2H, m, H-2′ and H-10), 1.52 (3H, s, H-15), 1.55 (1H, m, H-5), 1.73 (1H, m, H-5), 2.07−2.24 (4H, m, H-6 and H-9), 2.38 (1H, td, J = 12.9, 3.2 Hz, H-2′), 2.44 (1H, m, H-1), 3.32 (1H, dd, J = 13.1, 3.9 Hz, H-1′), 10.10 (1H, s, H-22), 10.12 (1H, s, H-23); ^{13}C NMR (methanol-d_4, 100 MHz) δ 15.1, 17.5, 18.2, 19.2, 20.9, 22.6, 23.5, 26.0, 26.7, 27.7, 29.7, 30.3, 35.6, 35.7, 37.1, 40.4, 48.9, 49.1, 104.5, 104.6, 109.9, 125.4, 138.3, 166.9, 168.7, 169.5, 191.5, 191.6; negative HRESMS m/z 453.2634 (calcd for $C_{28}H_{37}O_5$, 453.2641 [M − H]$^-$).

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR for compounds **2a**, **2b**, **3a**, and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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