The Total Synthesis of Robustadial A and B Dimethyl Ethers

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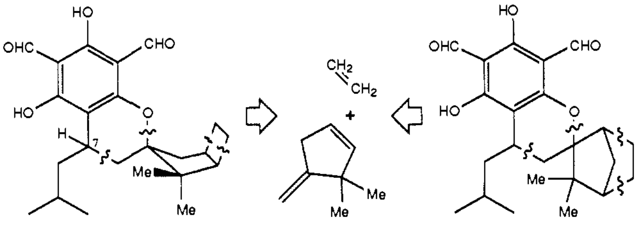
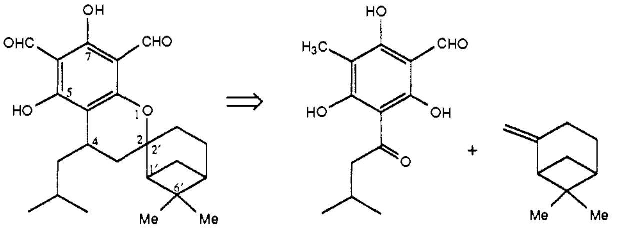
An urgent need for the identification and total synthesis of new antimalarials inspired a persistent quest to unravel the elusive structures of robustadials A and B, natural products isolated from the antimalarial Chinese herbal medicinal extract of *Eucalyptus robusta* leaves.[1] Herein we report the successful conclusion of our studies which now conclusively establish the correct structures by total syntheses from (+)-nopinone.



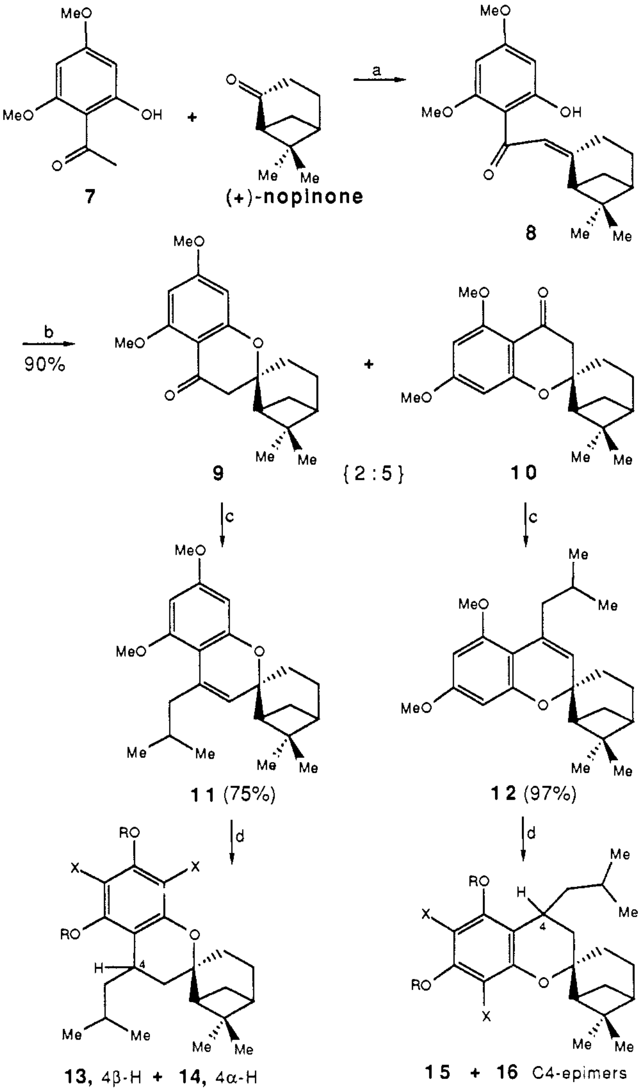
1a, 7α-H
1b, 7β-H
2
3



robustadials (4) **grandinol (5)** **β-pinene (6)**

The original presumption of bicyclo[3.2.0]heptyl structures **1a** and **1b** for robustadials A and B, respectively,[2] was refuted by total synthesis.[3] A prenylphenol-terpenoid biogenesis seemed likely since the aromatic acetogenin-isopentyl portion proposed for the robustadials is identical with that found in the euglobals, a family of biologically active compounds isolated from the buds and leaves of *Eucalyptus globulus*.[4] The observation of major fragments corresponding to ethylene and C_8H_{11} in the mass spectrum of robustadials misdirected attention toward a readily cleavable ethano moiety and a fragment **2**. Since mass spectral fragmentation of camphene generates similar major fragments, camphane analogues **3** of **1** were examined but shown by total synthesis not to correspond with the natural products.[5] An alternative hypothesis is that robustadials are pinane derivatives **4** which arise by addition of a prenylphenol moiety derived from the natural product grandinol (**5**)[6] to the C=C bond of *β*-pinene (**6**). Although the possibility for mass spectral generation of ethylene and C_8H_{11} is less evident, such fragmentation of **4** is virtually inevitable since cationic rearrangement in the mass spectrometer of the pinane segment to produce a camphane structure finds analogy in solvolytic rearrangements of pinanes.[7] Furthermore, *Eucalyptus robusta* leaves yield an oil consisting "largely of pinene".[8]

Scheme I[a]



	X = H, R = Me	**13a**(11%)	**14a**(86%)	**15a**(11%)	**16a**(66%)
e →	X = Br, R = Me	**13b**(90%)	**14b**(99%)	**15b**(98%)	**16b**(100%)
f-h →	X = CHO, R = Me	**13c**(69%)	**14c**(51%)	**15c**(64%)	**16c**(72%)
	X = CHO, R = H	**13d**	**14d**		

[a] (a) pyrrolidine/benzene/$-H_2O$; (b) K_3CO_3/90% EtOH/boil; (c) Me_2CHCH_2MgCl, then aqueous HCl; (d) H_2/Pd/C; (e) pyridine-Br_2/CH_2Cl_2; (f) *n*-BuLi/THF, then CO_2, then HCl, then CH_2N_2/Et_2O; (g) DIBAL-H/toluene; (h) PDC.

Since the cyclobutylcarbinyl ether array in **4** was expected to be acid-labile, synthetic methods for elaboration of chromanones involving acid catalysis were avoided. The robustadial ring system was assembled in one step by a pyrrolidine-catalyzed condensation[9] of (+)-nopinone with 2,4-dimethoxy-6-hydroxyacetophenone (**7**). Although a 2:5 mixture of chromanones **9** and **10**, respectively,

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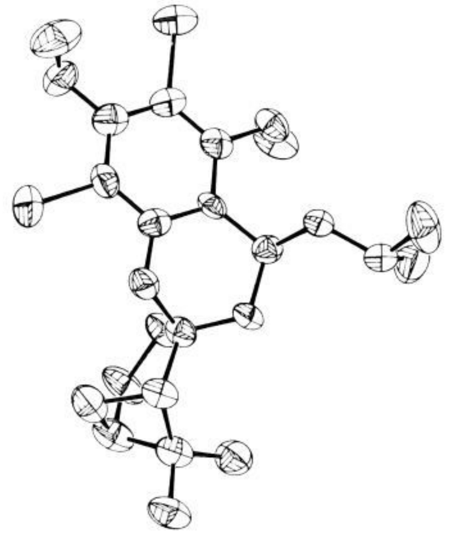

Figure 1. X-ray structure of **14b**.[13]

was obtained (20%), the major product isolated was the α,β-unsaturated ketone **8** (41%).[10] Cyclization of **8** was best achieved with base catalysis in ethanol which delivered a 2:5 mixture of **9** and **10** in excellent yield. Completion of the carbon skeleton was then achieved by appendage of an isobutyl nucleophile at the carbonyl carbon of **9** or **10** and dehydration of the resulting tertiary benzylic alcohol which delivered **11** or **12**, respectively. Catalytic hydrogenation of these alkenes provided the epimers **13a** plus **14a** from **11** and **15a** plus **16a** from **12** (see Scheme I).[11] The production of intractable mixtures containing a multitude of products upon attempted bromination of these intermediates with bromine in methylene chloride was attributed to their acid lability. This obstacle was surmounted by the use of pyridine perbromide.[12] The stereostructures of **9–12**, **13**, and **14** were unambiguously established by single-crystal X-ray analysis (Figure 1) of the crystalline dibromide **14b.** Conversion of the dibromides **13b–16b** into the corresponding dialdehydes **13c–16c** was accomplished by lithium–bromine exchange, carboxylation, methylation, reduction, and partial reoxidation. The ^1H and ^{13}C NMR spectra of **13c** and **14c** were identical with those of samples prepared by methylation of natural robustadials A and B, respecively. Further, a comparison of optical rotations and CD spectra of **13c** and **14c** with those of naturally derived robustadials showed that the absolute configurations of the (+)-nopinone-derived products are identical with those of the natural products. Therefore, the absolute stereostructures of robustadials A and B correspond to **13d** and **14d**, respectively.

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Supplementary Material Available: Tables of data collection details, fractional atomic coordinates, and anisotropic thermal parameters for non-hydrogen atoms of **14b** as well as analytical and spectral data for all new compounds (12 pages). Ordering information is given on any current masthead page.

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[10] ^1H and ^{13}C NMR analysis of **8** is consistent with this alkene being a single geometric isomer. An assignment of configuration has not been made. The epimers **9** and **10** were separated chromatographically (see Supplementary Material) prior to conversion to **11** and **12**, respectively.

[11] Each pair of epimers was separated by HPLC (see Supplementary Material).

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[13] X-ray analysis (Mo Ka radiation): **14b** crystallizes from methanol in the monoclinic space group $P2_1$ with $a = 10.685$ (1) Å, $b = 10.987$ (2) Å, $c = 11.312$ (1) Å, $\beta = 116.14$ (1)°, $V = 1192.15$ (31) Å^3, $Z = 2$. Standard direct and difference Fourier methods and least-squares refinement on the basis of 1366 reflections ($I \geq 3\sigma$) for 250 parameters led to final values of $R = 0.046$ and $R_w = 0.049$.

Low-Temperature Synthesis of Superconducting $La_{2-x}M_xCuO_4$: Direct Precipitation from NaOH/KOH Melts

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The new copper oxide superconductors, $La_{2-x}M_xCuO_4$ (M = Ca, Sr, Ba with $0.05 < x < 0.30$),[1] $RBa_2Cu_3O_7$ (R = Y or other lanthanide elements),[2] and $Bi_2Sr_2CaCu_2O_{8-y}$,[3] generally have been prepared by reactions of intimate mixtures of the metal oxides, carbonates, oxalates, or nitrates at high temperatures (often up to 1100 °C). Product homogeneity is enhanced either through repeated heating and grinding cycles or by coprecipitation of the individual metal salts from aqueous solutions prior to high temperature processing. Disadvantages of this synthetic route include the following: (1) inhomogeneities in the products due to imperfect grindings or to the dissimilar precipitation rates of the salts of rare-earth, alkaline-earth, and copper ions; (2) impurities in the products introduced by multiple grindings and firings; and (3) high cost due to high-temperature processing for extended times. Clearly, there is a need to discover new synthetic routes to copper oxides. Our strategy utilizes molten salts to dissolve the starting materials and directly precipitate the final product. This laboratory has shown previously that single crystals of new barium copper oxides can be prepared from $Ba(OH)_2/BaCl_2$ melts at temperatures above 650 °C.[4] Here, we report the synthesis of superconducting $La_{2-x}M_xCuO_4$ (M = Na, K, or vacancy) from NaOH and KOH melts at 300 °C. This route offers the advantages of a single-step preparation of the product at temperatures much lower than those used in previous syntheses; La_2CuO_4 is prepared typically between 900 °C and 1100 °C.

Fused hydroxides are ideal for the preparation of rare-earth–copper oxide superconductors because these solvents melt at low temperatures, dissolve metal oxides, and stabilize high oxidation states. Synthesis at temperatures lower than those required for direct reaction is possible in fused hydroxides since NaOH and KOH melt at 318 °C and 360 °C, respectively, and an equimolar mixture at 170 °C. Molten hydroxide is a Lux–Flood acid–base solvent system, with OH^- in equilibrium with its conjugate acid, H_2O, and its conjugate base, O^{2-}. Melts can be made more acidic (H_2O-rich or low pH_2O) or basic (O^{2-}-rich) by controlling the water content of the melt. Since the equilibrium concentrations of the dissolved phases of a metal oxide depend on the oxide ion concentration, precipitation of products can be controlled by changing the water concentration of the melt. Finally, the electrochemical-potential window of the hydroxide melts is large enough to allow the existence of metals and oxygen in various oxidation states.[5] In particular, high oxidation states such as O_2^- and O_2^{2-} are stable, and the presence of Cu^{3+} has been reported.[5,6] This is important because all of the copper oxide superconductors

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