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Communications

Stereoselective Synthesis of Precursors of Naturally Occurring Robustadials A and B

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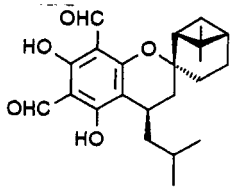
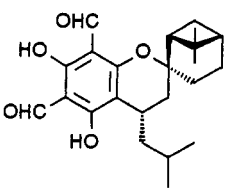
Summary: The key intermediates of robustadials A and B have been synthesized in a new and stereoselective synthesis with high overall yields starting from (*S*)-(−)-β-pinene and readily available materials; after bromination of one stereoisomer the absolute configuration was established by X-ray diffraction analysis.

The robustadials are naturally occurring antimalarial compounds isolated from the ethanolic extracts of the leaves of *Eucalyptus robusta*. Nakanishi et al.[1] first proposed structures for robustadial A and B. The structure



1a Robustadial A



1b Robustadial B

was soon questioned by Salomon[2] who, together with Snyder et al.,[3] revised the structure. Salomon[4] also provided the first total synthesis and demonstrated the identity of the synthetic material with naturally occurring robustadial A and B by comparison of extensive data, including CD spectra. The structures were assigned by X-ray diffraction analysis of a synthetic dibromo precursor (see discussion below).

We reasoned that the tetracyclic skeleton of robustadial should be accessible directly and efficiently from naturally occurring (*S*)-(−)-β-pinene and cycloaddition to an 1-oxabutadiene species, generated as a reactive intermediate. In our approach, the choice of the β-pinene (either *S* or *R*) determines unequivocally the absolute configuration of the key spirocenter in the robustadial (Scheme I).

The first step consists of a one-pot preparation of spiro ether **2**.[5] This tandem cyclocondensation[6] involves an aldol addition with dehydration (Knoevenagel) followed by a hetero-Diels–Alder reaction[7] with inverse electron demand. The reaction conditions of this step were carefully optimized,[8] in order to suppress the accumulation of undesired

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(1) Xu, R.-S.; Snyder, J. K.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 734.

(2) Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1311.

(3) Cheng, Q.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 4562.

(4) (a) Salomon, R. G.; Lal, K.; Mazza, S. M.; Zarate, E. A.; Youngs, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 5213. (b) Salomon, R. G.; Mazza, S. M.; Lal, K. *J. Org. Chem.* **1989**, *54*, 1562. Cf. also: Majewski, M.; Bantle, G. *Tetrahedron Lett.* **1989**, *30*, 6653.

(5) Experimental procedure: A 250-mL flask fitted with reflux condenser was charged with 5-(methoxycarbonyl)cyclohexane-1,3-dione (14.7 g, 86.3 mmol), isovaleric aldehyde (14.9 g, 173 mmol), (1*S*)-β-pinene (47 g, 345 mmol), KOAc (0.85 g, 8.7 mmol), catalytic hydroquinone, and molecular sieves (15 g) in acetic acid (50 mL) under N_2. The mixture was stirred at 100 °C for 20 h and cooled, and the solvent was removed. The residue was taken up with CH_2Cl_2, filtered over Celite, and washed with saturated $NaHCO_3$ solution (2×) and brine. The red organic phase was dried ($MgSO_4$), and the solvent was removed. Column chromatography (cyclohexane/EtOAc (3:1)) afforded **2**, white solid (26 g, 80%).

(6) Recent reviews: Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137. Boger, D. L.; Weinreb, S. N. *Hetero-Diels–Alder Methodology in Organic Synthesis*; Academic Press Inc.: San Diego, 1987. Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992.

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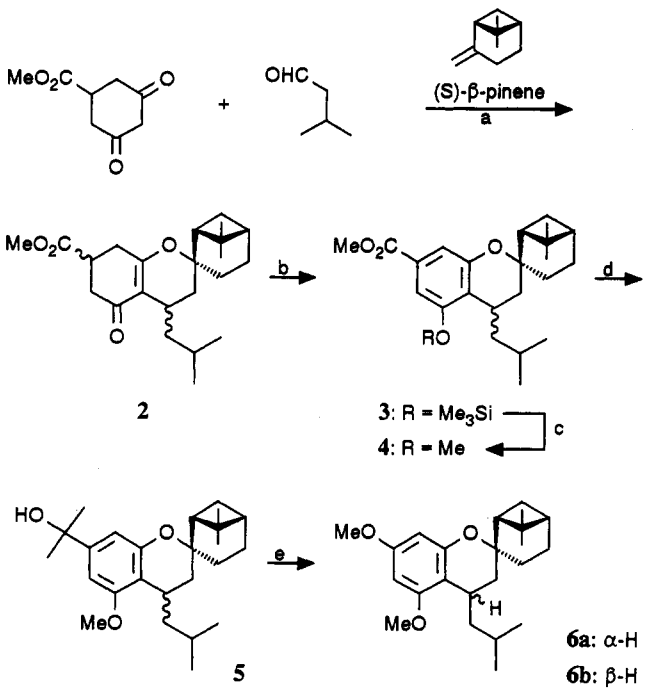
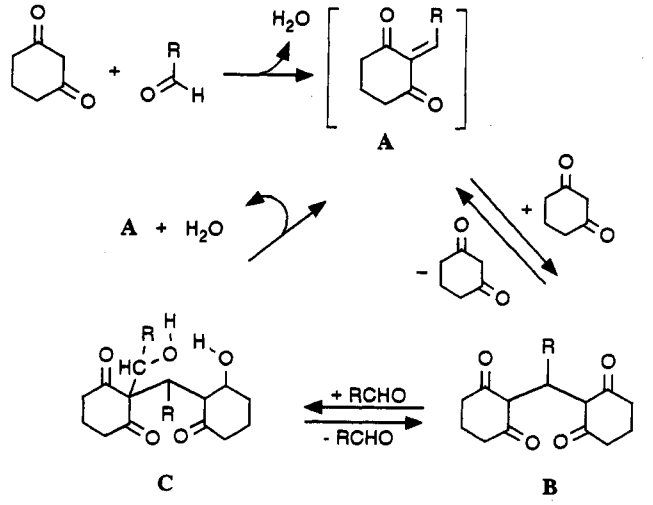
Scheme I[a]



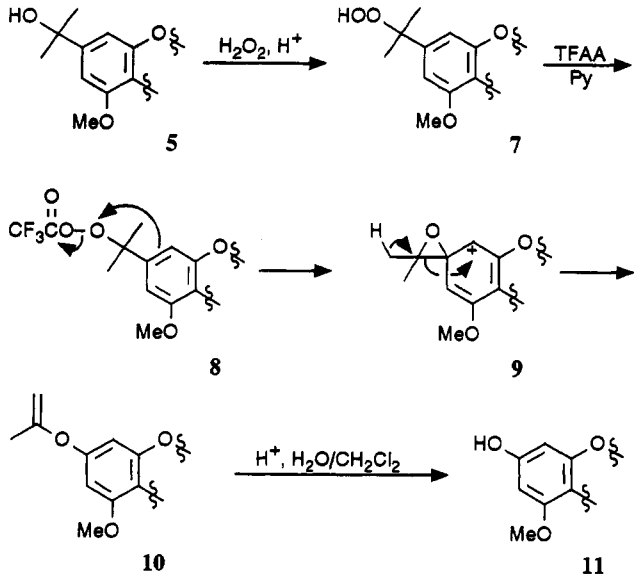
[a]Key: (a) HOAc (1.8 M), KOAc (0.1 equiv), hydroquinone (cat.), MS 3 Å, 100 °C, 20 h, 80%; (b) BSA (bis(trimethylsilyl)acetamide) (6 equiv), DDQ (3 equiv), degassed dioxane (1 M), 110 °C, 1 h, 63%; (c) (1) DMF, KF (2 equiv), 48% HBr_{aq} (0.3 equiv), rt, 0.5 h, (2) acetone, $(MeO)_2SO_2$ (2.5 equiv), anhyd K_2CO_3 (3 equiv), 50 °C, 1.5 h, 85%; (d) ether, MeMgI (3 equiv), reflux, 3 h, 98%; (e) (1) ether 85% H_2O_2 (20 equiv), *p*-TsOH (0.1 equiv), rt, 6.5 h, (2) CH_2Cl_2, py (1 equiv), $(CF_3CO)_2O$ (1 equiv), 0 °C, 5 min, (3) CH_2Cl_2/H_2O (4:1), CF_3CO_2H (1.3 equiv), 0 °C, 3 h, (4) acetone, $(MeO)_2SO_2$ (2 equiv), anhyd K_2CO_3 (1.6 equiv), rt, 17 h, 74% over all four steps.

Scheme II



Michael adduct **B**[9] (Scheme II). In fact, combination of **B** with a second molecule of aldehyde and then loss of one molecule of water (**B** + RCHO → **C** → H_2O + 2**A**) regenerates the desired reactive intermediate **A** with proliferation[10] (cf. also Smith).[11] Thus, formation of Michael adduct **B** and aldol bisadduct **C** is not a problem under optimized reaction conditions, since intermediate **A** is recycled efficiently.

Scheme III. Oxidative Route to Electron-Rich Phloroglucinols



Note also that the hetero-Diels–Alder reaction is regioselective because the oxygen of the oxabutadiene moiety **A** attacks only the disubstituted terminus of the pinene double bond. More importantly, the reaction is stereoselective with respect to the absolute configuration of the spirocenter in that the oxabutadiene approaches the β-pinene double bond exclusively from the π-face opposite the geminal dimethyl bridge. Thus, tetracycle **2** is built up with three defined stereocenters (spiro center and two bridgehead centers via (*S*)-β-pinene). The aromatization step (**2** → **3**) was tried with a number of methods [α-selenenylation–oxidation,[12] α-halogenation,[13] α-hydroxylation[14] (dimethyloxirane)] but failed completely or gave unacceptable yields. DDQ in dioxane solvent alone was also unsuccessful. A Merck Sharpe & Dohme group has shown that DDQ and bis(trimethylsilyl)acetamide (BSA) are advantageous for dehydrogenation of lactones to α,β-unsaturated lactones.[15] In the presence of excess BSA the desired tetracyclic silyl ether **3** was formed in 63% yield. We interpret that BSA functions as Lewis acid on the one hand and on the other hand as a reagent which drives the thermodynamic equilibrium to the aromatic product by *O*-silylation.

(7) Cf. Ismail, Z. M.; Hoffmann, H. M. R. *Angew. Chem.* **1982**, *94*, 864. Krause, M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1990**, *31*, 6629. Daude, N.; Eggert, U.; Hoffmann, H. M. R. *J. Chem. Soc., Chem. Commun.* **1988**, 206. Hoffmann, H. M. R.; Vogt, U. *Synlett* **1990**, 581. Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098.

(8) Koser, S. PhD thesis, University of Hannover, 1993. Concentrations of reactants, reaction temperature, solvent, drying agent, and reaction time were optimized. Hetero-Diels–Alder reactions with naturally occurring terpenes other than β-pinene have recently been accomplished: Koser, S.; Hoffmann, H. M. R. *Heterocycles*, in press.

(9) In a typical experiment the consumption of the 1,3-cyclohexandione is complete after 3 min with mainly formation of **B** (TLC).

(10) Fortunately, the ene reaction of the oxabutadiene **A** as an enophile with β-pinene was insigificant, although as a strained 1,1-dialkylated ethylene derivative, β-pinene is an ene component par excellence, especially at higher temperature (Hoffmann, H. M. R. *Angew. Chem.* **1969**, *81*, 597). In contrast, the oxabutadiene generated from *formaldehyde* and 1,3-cyclohexanedione gave 41% ene product at 60 °C.

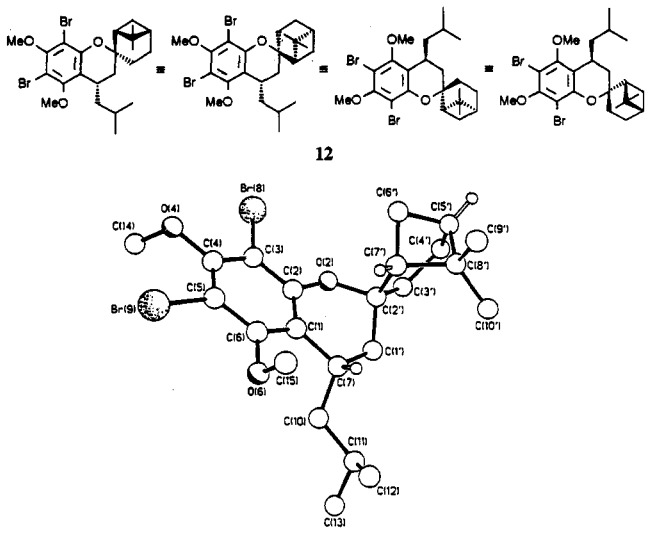
(11) Buzinkai, J. F.; Hrubowchak, D. M.; Smith, F. X. *Tetrahedron Lett.* **1985**, *26*, 3195.

(12) Nicollier, G.; Rebetez, M.; Tabacchi, R.; Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1978**, *61*, 2899.

(13) Blanco, L.; Amica, P.; Conia, J. M. *Synthesis* **1976**, 194.

(14) Adam, W.; Bialis, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(15) Bhattacharya, A.; DiMichele, L. M.; Dolling, U.-H.; Douglas, A. W.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 3318.



12

Figure 1. X-ray crystal structure of 12 and projection formulas.

Conversion of the silyl ether into the methyl ether 4[16] and formation of the tertiary alcohol 5 were straightforward. The scene was now set for the conversion of the resorcinol ether 5 into the electron-rich phloroglucinol derivative 6. In our case, the useful one-pot procedure ofBoger[17] (H_2O_2 90%, BF_3·OEt_2) was not successful, presumably because of further oxidation of the phloroglucinol (formation of black tar at 0 °C). Apparently, these conditions are too drastic and the electron-rich phloroglucinol, if formed at all, is exposed to further oxidation by H_2O_2.

We reasoned that the seemingly straightforward nucleophilic migration of the aryl group was impeded by the *two wrongly positioned* alkoxy groups. Put another way, from the point of view of the electrophilic oxygen cation, the required intramolecular ipso attack of the aromatic nucleus with generation of the spiro epoxide 9 is unfavorable because of the two *deactivating* meta alkoxy substituents[18] (Scheme III).

On the other hand, for the same reason the substituted cumyl hydroperoxide 7 could be isolated, even under acidic conditions (Scheme I, step e, and Scheme III). Activation of the hydroperoxide group with trifluoroacetic anhydride brought about the desired intramolecular electrophilic attack of the resorcinol derivative (8 → 9). In this fashion, the phloroglucinol 11 never came into contact with strongly oxidizing reagents such as 90% H_2O_2. In practice, the transformation of 5 into 6 was carried out in excellent yield without isolation of the intermediates.[19] Alternatively, under anhydrous conditions, enol ether 10 was isolated and could easily be hydrolyzed to 11. To our knowledge, this is the first time that an enol ether has been isolated in a Baeyer–Villiger-type rearrangement.[20]

We obtained two diastereomers 6a,b which had ^{13}C and ^{1}H NMR spectra identical to the literature.[4b,21] Specifically, the diagnostic ^{13}C chemical shift of the chiral spirocarbon center (81.51 in one diastereomer and 81.08 ppm in the other) and that of the neighboring bridgehead carbon (47.26 and 50.62 ppm, respectively) compared very favorably with the data reported (81.52 and 81.01; 47.22 and 50.55 ppm).[4b,21] The 81.51/47.26 diastereomer 6b was converted into the dibromide, the structure and the absolute configuration of which were determined by X-ray diffraction (Figure 1).[22] This structure is identical to the projection formula 12.[23] However, the benzylic hydrogen of our 81.51/47.26 diastereomer is β (the isobutyl group is α) instead of being α as described in the literature.[24]

In conclusion, we have carried out an efficient, eight-step synthesis of the two robustadial A and B precursors 6a,b in 31% combined yield.[25] We hope that our work will help to clarify and remove the apparent confusion that currently surrounds the structures of the robustadials. Finally, the occurrence of *both* robustadials in nature accords with the idea that our synthesis proceeds along biogenetic lines with a hetero-Diels–Alder reaction as key step.

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Supplementary Material Available: Experimental procedures and compound characterization data (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(16) The nonmethylated phloroglucinol was isolated in 11% yield.

(17) Boger, D. L.; Coleman, R. S. *Tetrahedron Lett.* **1987**, *28*, 1027.

(18) While an alkoxy group ortho to the ipso carbon and also para (Hammett $\sigma_{p\text{-methoxy}} = -0.28$) would have been favorable for formation of the spiro intermediate, the two meta-oriented alkoxy groups are, of course, unfavorable (Hammett $\sigma_{m\text{-methoxy}} = 0.1$).

(19) After each step only a short aqueous workup was necessary to remove salts and excess reagents. Only after the last step the compound was purified by column chromatography.

(20) See Krow, G. R. *Org. React.* **1993**, *43*, 251.

(21) Cf. supplementary data. The other ^{13}C signals agreed also very well with those reported.[4]

(22) Crystal data: $C_{23}H_{32}Br_2O_3$, $M_w = 516.3$, monoclinic, $a = 9.433(2)$ Å, $b = 12.222(2)$ Å, $c = 11.155(2)$ Å, $\beta = 113.61(2)°$, $V = 1178.4(3)$ Å^3, space group $P2_1$, $Z = 2$, $D_c = 1.46$ g cm^{-3}, $\mu = 45.2$ cm^{-1}, $F(000) = 528$. 1679 independent reflections ($\theta < 58°$) were measured on a Siemens P3/PC diffractometer with Cu–K_α radiation (graphite monochromator) using ω-scans. Of these 1638 $|F_o| > 4\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarization factors, and a numerical absorption correction was applied (maximum and minimum transmission factors 0.516 and 0.263). The structure was solved by direct methods, and the non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were idealized C–H = 0.96 Å, assigned isotropic thermal parameters $U(H) = 1.2U_{eq}(C)$, and allowed to ride on their parent carbon atoms. Refinement was by full-matrix least-squares methods to $R = 0.032$, $R_w = 0.038$ ($w^{-1} = \sigma^2(F) + 0.0005F^2$). The absolute stereochemistry was determined by an R-factor test ($R^+ = 0.0323$, $R^- = 0.0340$) and by refinement of a free variable η which multiplies all f'' (this variable refined to a value of 1.27(9)). Computations were carried out on a 486 PC using the SHELXTL-PC program system. Atomic coordinates, bond lengths, angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(23) It is easy to confuse the absolute configuration of the chiral centers. Although the four projection formulas may look different, they depict the identical molecule.

(24) Inspection shows that the absolute X-ray structure of the dibromide in the literature (see ref 4a, Figure 1) and the given projection formula (*Ibid.*, formula 14b) are in an enantiomeric relationship. Since the authors started from (+)-nopinone, the projection formula has the correct absolute configuration and the X-ray structure must be inverted. In our dibromide the absolute stereochemistry of the pinane moiety was identical to the absolute stereochemistry of the starting (S)-(−)-β-pinene, as required.

(25) HPLC (reversed phase, spherisorb S5 ODS 2 packing, 200 mg of substance) allowed separation. Dibromide 12 was prepared from 6b according to the literature.[4b]