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STEREOSELECTIVE CONSTRUCTION OF THE RING SYSTEM OF ROBUSTADIALS

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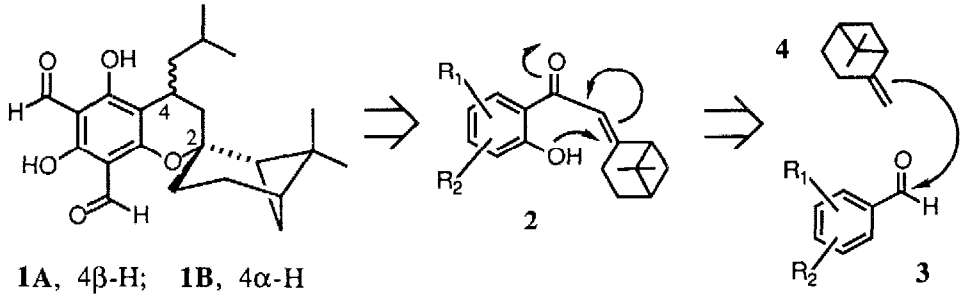
Summary: The spiro[3,4-dihydro-2H-1-benzopyran-2,2'-bicyclo[3.1.1]heptane] framework of natural products Robustadials was constructed in a homochiral form. The synthesis started from 1S-(-)-β-pinene, which was coupled to a substituted benzaldehyde using a Prins reaction, and incorporated a diastereoselective, Michael-type, intramolecular addition.

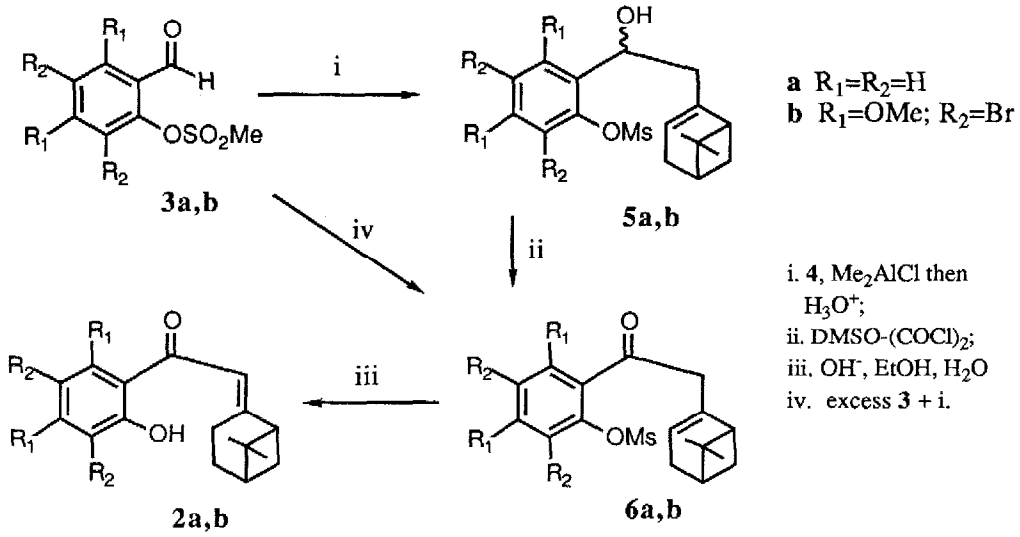
Robustadials A and B (**1**) have been isolated from *Eucalyptus robusta* leaves and are of interest as potential antimalarial drugs. The structure of these compounds has recently been firmly established by total synthesis coupled with X-ray crystallography and extensive NMR studies.[1] The most difficult transformation in a synthesis of Robustadials is the stereoselective construction of the spiro ring junction at the 2 position. In this letter we present a stereoselective synthesis of the key intermediate **7b** leading to Robustadials.



1A, 4β-H; **1B**, 4α-H

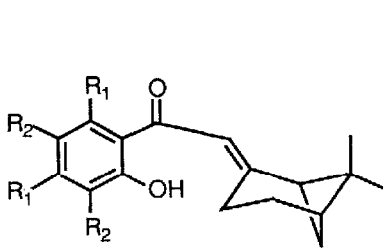
We envisaged the synthesis of Robustadials *via* intramolecular ring closure in a ketone **2**, the carbon skeleton of which would be constructed from β-pinene **4** and the appropriately substituted benzaldehyde **3**. The isobutyl side chain at the 4 position and the required substituents on the aromatic ring will be added at later stages in the synthesis.

The synthesis of ketones **2a** and **2b**, which were used to study the stereochemistry of cyclization, is presented below:

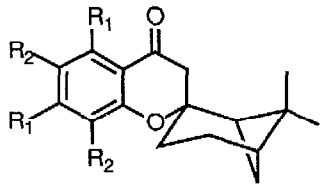


The Prins reaction[2a] between mesyl salicylaldehyde **3a** and 1S-β-pinene **4**, in the presence of dimethylaluminum chloride, produced the alcohol **5a** in 93% yield. Interestingly, when the reaction was conducted with an excess (2.1 eq.) of the aldehyde **3a**, the ketone **6a** was produced directly (presumably *via* an *in situ* Oppenauer oxidation[2b]) in 90% yield. This, in fact, proved to be the most convenient method for synthesis of **6a**. Ketone **6b** was produced in the two step procedure (second step: a Swern oxidation of the alcohol **5b**, which was isolated in 50% yield and purified); the *in situ* oxidation in this case was very inefficient (less than 10% yield). Upon treatment with NaOH in aqueous ethanol (**6a**) or with Na_2CO_3 in 95% ethanol (**6b**) the ketones **2a** (75% yield) and **2b** (80% yield) were obtained.[3]

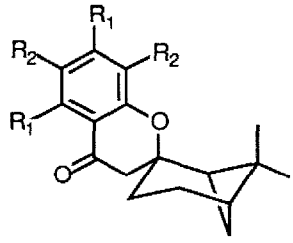
The stage was now set for investigation of the ring closure. Attempts to cyclize **2a** under acidic conditions or *via* oxymercuration or halogenation were unsuccessful. Applying the conditions most often used in an oxy-Michael-type reaction, namely Na_2CO_3 in ethanol at elevated temperature for a long time, we observed the formation of two isomeric cyclic compounds **7a** and **8a** in a ratio of 29:71. This was in agreement with the report of Salomon and coworkers involving similar compound.[1a] We noticed, however, that when the cyclization was stopped at a low conversion (<10%) **7a** was the major product. This lead us to belive that **7a** (which has the stereochemistry identical with Robustadials) is the kinetic product and **8a** is the thermodynamic product of the reaction.



2a,b



7a,b



8a,b

Thus we were faced with an interesting situation: a necessity to maximize the formation of a kinetic product in a reaction which is perceived to be thermodynamically controlled, since it involves a counterthermodynamic alkoxide (or phenoxide) to enolate transformation.[4] We reasoned that the stereoselectivity should be dependent on the base used. The base should be weak enough not to allow a fast retro-Michael reaction; at the same time the rate of protonation of the enolate by the conjugated acid of the base should be maximized. We investigated a number of bases; the results are presented in Table1.

Table 1: Cyclization of **2a** and **2b** under basic conditions.

Entry	Compound	Base/Solvent	**7 : 8**[a]	Yield (%)[b]
1.	**2a**	Na_2CO_3 / EtOH	29 : 71	80
2.	"	Cs_2CO_3 / EtOH	29 : 71	80
3.	"	NaOH / EtOH	50 : 50	10
4.	"	$NaHCO_3$-Na_2CO_3 / EtOH	33 : 67	84
5.	"	PhONa / EtOH	37 : 63	75
6.	"	Et_3N / DMSO	40 : 60	70
7.	"	Et_3N / EtOH	>96 : 4[c]	60
8.	**2b**	Na_2CO_3 / EtOH	50 : 50	10
9.	"	Et_3N / EtOH	54 : 46	75
10.	"	Piperidine / EtOH	33 : 67	70
11.	"	Morpholine / EtOH	83 : 17	84
12.	"	DMAP / EtOH	66 : 34	90
13.	"	Proton Sponge / EtOH	60 : 40	90

a. The ratio was determined by NMR after work-up and purification by chromatography.
b. Isolated yield. c. The product **7a** pure by NMR was obtained; the 4% level of detection of **8a** has been assumed.

When sodium carbonate (entry 1) was used in the cyclization reaction of **2a** the more stable product **8a** predominated. The use of sodium hydroxide (entry 3) resulted in a very low

yield and lack of stereoselectivity. A buffer solution (entry 4) yielded slightly more of **7a** than did the more basic Na_2CO_3 (entry 1). Sodium phenoxide in ethanol (entry 5) produced a similar result. We then turned our attention to bases less frequently used in Michael reactions: cesium carbonate and amines.[5] While the former behaved analogously to sodium carbonate, the latter generated excellent stereoselectivity. Thus the cyclization with triethylamine in ethanol (entry 7) resulted in the formation of **7a** pure by NMR!

The substituted phenol **2b**, with the functional groups on the aromatic ring necessary for synthesis of Robustadials, is more acidic than **2a**. This was reflected in the cyclizations of this compound. When Na_2CO_3 or Et_3N were used as bases the cyclization was non-stereoselective (entries 8 and 9). Using piperidine, which is more basic than triethylamine, resulted in even smaller amount of the kinetic product **7b** being formed (entry 10). However, morpholine, less basic than Et_3N, afforded highly stereoselective cyclization in which the desired kinetic product **7b** predominated (entry 11). The trend is clearly apparent; the weaker the base the more selective the reaction.

The synthesis of Robustadials from compound **7b** is well precedented.[1a] The details of the complete synthesis will be presented in a full paper.

References and footnotes:

1. a. Synthesis: Salomon, R. G.; Lal, K.; Mazza, S. M.; Zarate, E. A.; Youngs, W. J. *J. Am. Chem. Soc.* **1988**, 110, 5213. b. NMR studies: (i) Cheng, Q.; Snyder, J. K. *J. Org. Chem.* **1988**, 53, 4562.(ii) Salomon, R. G.; Mazza, S. M.; Lal, K. *ibid.* **1989**, 54, 1562.
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3. The *E* isomer only was obtained in each case.
4. For a different solution to a similar problem (the kinetic vs. the thermodynamic product in an oxy-Michael-type intramolecular addition) see: Guindon, Y.; St. Denis, Y.; Daigneault, S.; Morton, H. E. *Tetrahedron Lett.* **1986**, 27, 1237.
5. a. Cesium carbonate was successfully used in intramolecular Michael additions by Deslongchamps and co-workers; see eg. Lavallee, J.-F.; Deslongchamps, P. *ibid.* **1987**, 28, 3457. b. The use of amines in Michael-type reactions is well precedented: (i) House, H. O. *"Modern Synthetic Reactions"* 2nd ed., Benjamin, Menlo Park, California, **1972**, p. 597. (ii) Varma, R. S.; Kadkhodayan, M.; Kabalka, G. W. *Synthesis* **1986**, 486. c. We thank Professor Deslonchamps for a stimulating discussion concerning the Michael reaction.

6. The financial support from NSERC Canada is gratefully acknowledged.

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