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MODEL STUDIES ON THE SYNTHESIS OF THE NATURAL MEROTERPENOID CORDIAQUINONE A

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ABSTRACT: Two main strategies for the synthesis of the natural meroterpenoid *cordiaquinone A* (1) - isolated of the roots of *Cordia corymbosa* G. Don (Boraginaceae) - were tested on model compounds. Whereas all attempts of alkylation of e-caprolactone (10) were unsuccessful, the coupling of epoxycitronellol (17) with an appropriate organocuprate proceeded in the expected direction.

KEYWORDS: Meroterpenoid naphthoquinone, *Cordia corymbosa*, Boraginaceae, e-caprolactone, epoxycitronellol, organocuprate.

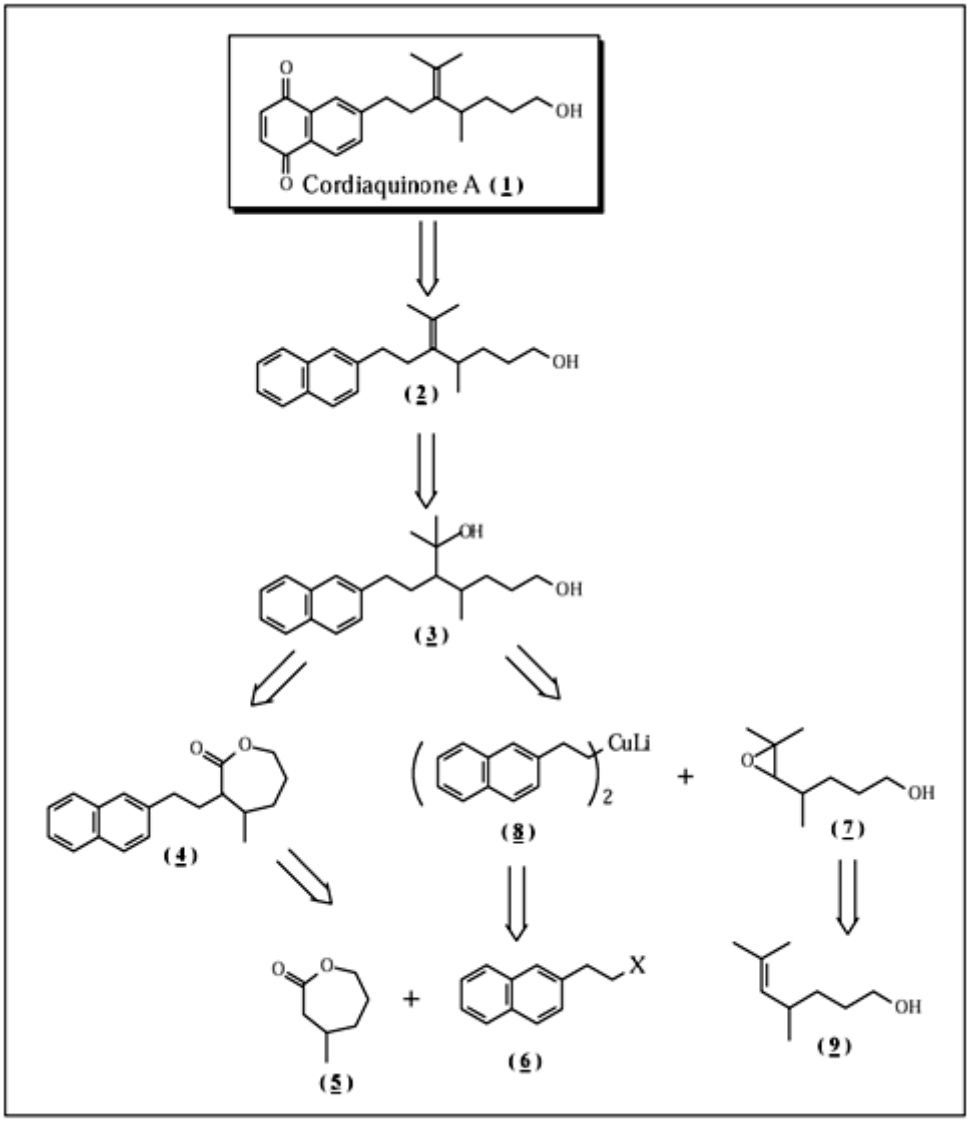
INTRODUCTION

Cordiaquinone A (1) is the most abundant of a new type of meroterpenoid naphthoquinones found in the roots of *Cordia corymbosa* G. Don, popularly known as "maria preta".[2,3] The unique rearranged terpenoid skeleton of still unknown absolute configuration represents an interesting challenge for an asymmetric total synthesis which should start with a simple, enantiomerically pure and easily available compound. A first retrosynthetic analysis *(scheme 1)* suggested the unfunctionalizated naphthalene (2) as the most suitable precursor because of the availability of a number of simple 2-substituted naphthalenes which could be used as building blocks. However, the final oxydation (probably by Ce^{4+}) is not expected to be regioselective.[12] For the next step, the introduction of a tetrasubstituted olefinic double bond, a Wittig-reaction was not considered because of the risk of epimerization a to the carbonyl group in the case of the use of pure enantiomers. Water elimination from the tertiary alcohol (3) seemed more reliable. This diol offers two very short alternatives of disconnection to simple starting materials:

1. The addition of methyl lithium to a carboxylic intermediate, ideally the substituted

lactone (4) which should be accessible from 3-methyl-e-caprolactone (5) and a suitable alkylating agent (6).[1,7] Both pure enantiomers of (5) have been prepared before from pulegone.[8]

2. The nucleophilic ring opening [10] of the epoxide (7) with a conjugate cuprate (8) derived from (6). (7) may be obtained from the known unsaturated alcohol (9), previously described as a subproduct of a multistep procedure starting from b-pinene.[13]



SCHEME 1

MATERIAL AND METHOD

Melting points are uncorrected. NMR^{1}H spectra were recorded on a VARIAN EM 390 instrument at 90 MHz. IR spectra were obtained on a BRUKER FTIR IFS 66 spectrometer. THF was distilled over metallic potassium before use. All new compounds – (6) (X = I), (12), (13), (15) and (18) – gave satisfactory elemental analyses.

2-(2-Iodoethyl) naphthalene (6 , X = I):

3.0 mmol (0.45 g) of sodium iodide and 3.0 mmol (0.97 g) of toluenesulfonate (6) (X = OTos) [1] were stirred in 10 mL of acetone in the dark. After 3 days, 30 mL of hexane were added and the mixture was allowed to stand for 2 h. The precipitate was filtered off and the solvent was evaporated. The residue was recrystallized from 15 mL of hexane. Yield: 0.65 g (77%) of colourless needles, m.p. 82-83° C. NMR^{1}H (CCl_4) d: 3.45 (s, 4H); 7.30-8.10 (m, 7H).

3-Methoxycarbonyl-2-oxepanone (12):

To a solution of 20.0 mmol (2.8 mL) of dry diisopropylamine in 20 mL of THF, at 0° C, were added 20.0 mmol (8 mL) of n-BuLi in hexane. The solution was cooled to -78° C and 10.0 mmol (1.14 g) of e-caprolactone (10) were added followed, after 30 min., by 10.0 mmol (0.8 mL) of methyl chloroformiate. After 1 h at -78° C, the temperature was allowed to rise to -30° C and quenched with 2 mL of glacial acetic acid. The solution was diluted with water and extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried over Na_2SO_4 and evaporated. The oily residue was purified over a silica gel column using toluene containing 5-10% of EtOAc as eluent. Yield: 0.318 g (18.5%) of yellowish oil. NMR^{1}H (CCl_4) d: 1.63-2.10 (m, 6H); 3.53-3.87 (m, superimposed to 3.77 (s) - total 4H); 4.17-4.43 (m, 2H).

2-Trimethylsilyloxy-2-oxepene (13):

To a solution of 12.0 mmol of the enolate of (10) in 10 mL of THF, prepared as described before, were added 12.0 mmol (1.5 mL) of chlorotrimethylsilane at -78° C. The mixture was allowed to warm to 0° C, hydrolyzed with 100 g of crushed ice and extracted with hexane (3 x 20 mL). The combinade extracts were washed with water and dried over K_2CO_3. After evaporation of the solvent, the product was distilled in vacuo. Yield: 0.649 g (34.9%) of colourless liquid, b.p. 65-67° C (1mm). NMR^{1}H (CCl_4) d: 0.62 (s, 9H); 1.83-2.77 (m, 6H); 4.00-4.23 (m, 3H).

3-Allyl-2-oxepanone (15):

To a solution of 15.0 mmol of the enolate of (10) in 15 mL of THF, prepared as described for (12), were added 15.0 mmol (1.4 mL) of allyl iodide at -78° C. After 1 h at this temperature, the solution was allowed to warm up to -30° C and quenched with 1 mL of glacial acetic acid. The mixture was diluted with water and extracted with CH_2Cl_2 (3 x 20 mL). The combinade extracts were washed with $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated. Flash distillation of the remaining oil yielded 0.679 g (26.6%) of colourless oil, b.p. 115-117° C (1mm). NMR^{1}H (CCl_4) d: 1.13-2.03 (m, 7H); 2.30-2.80 (m, 2H); 4.20 (m, 2H); 4.93-5.27 (m, 2H); 5.53-6.10 (m, 1H).

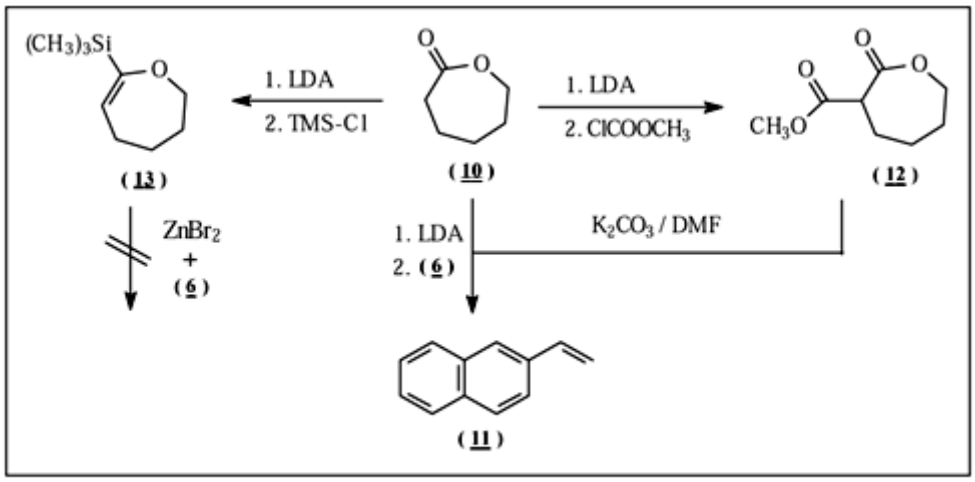
3,7-Dimethyl-6-[2-(2-naphthyl)ethyl]octane-1,7-diol (18):

To a solution of 1.0 mmol (0.282 g) of (6) (X = I) in 5 mL of THF was added, at room temperature, an excess of metallic lithium. The reaction was started by sonication for 2 min and then stirred for 3 h at 0° C. During this time, 0.5 mmol (0.095 g) of cooper (I) iodide were suspended in 2 mL of THF and 0.25 mmoL (0.040 g) of epoxycitronellol (17) and 0.25 mmol (0.1 mL) of n-BuLi were added at

-50° C. After 10 min., at -50° C, the lithium reagent prepared previously was added by means of a syringe, avoiding the excess of unreacted lithium metal. On rising the temperature slowly to -10° C, a green, homogeneous solution was formed which was kept for 2 days at -7° C. The reaction was hydrolyzed with saturated NH_4Cl solution and extracted with CH_2Cl_2 (3 x 20 mL). After drying over Na_2SO_4 and evaporation, the crystalline residue was purified on a silica gel column eluting initially with pure cyclohexane, then cyclohexane/toluene mixtures and at least pure toluene. The less polar fractions yielded 0,097 g of 1,4-di-2-naphthylbutane as colourless needles, m.p. 153-154° C (lit.[5] : 155-156° C). The toluene fractions yielded 0,047 g (57.3% based on (17)) of diol (18) as colourless prisms, m.p. 60-61° C. NMR^{1}H ($CDCl_3$) d: 0.90 (d, 3H, J=6Hz); 1.21 (s, 3H); 1.24 (s, 3H); 1.36-1.83 (m, 12H); 2.60-2.97 (m, 2H); 3.67 (t, 2H, J=6Hz); 7.27-7.97 (m, 7H). IR (KBr) cm^{-1}: 3379; 3051; 2925; 1631; 1600; 1053; 790; 750.

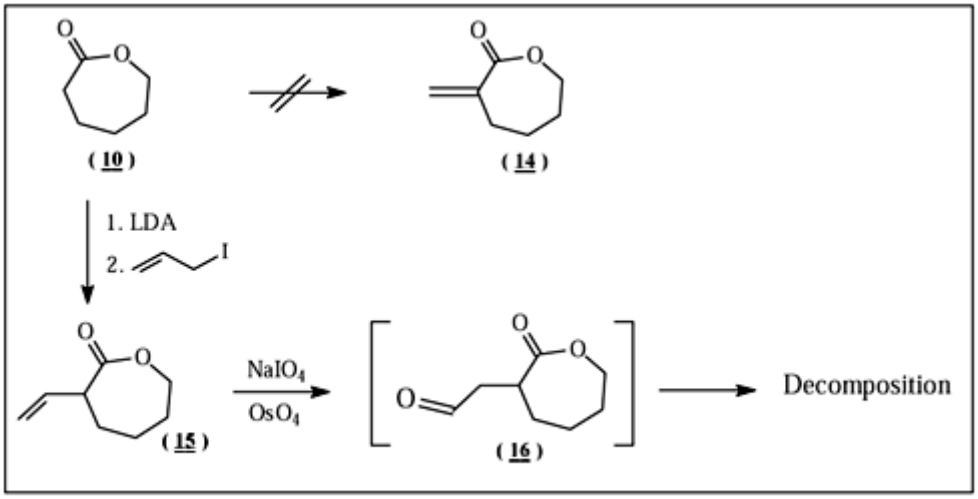
RESULTS AND DISCUSSION

Because of the difficult obtention of both starting materials, (5) and (9), we examined initially the feasybility of the first strategy using unsubstituted e-caprolactone (10) as model compound *(scheme 2)*. All attempts of direct alkylation of the enolate derived from (10), using THF, HMPA and their mixtures at temperatures between -78 and -30° C, produced only 2-vinylnaphthalene (11). At higher temperature occurred some Claisen condensation, but no substitution product was observed. In order to reduce the basicity of the enolate, we prepared the activated lactone (12). Its reaction with (6) (X = OTos and I) – even under very smooth conditions – led once more to the elimination product (11). In the hope that Lewis acid catalyzed alkylation could circumvent this problem,[11] the silylated derivative (13) was prepared, but it proved to be unreactive towards all available alkylating reagents (6) (X = OTos, Br and I) in the presence of zinc bromide in dichloromethane at room temperature. The more reactive titanium tetrachloride caused decomposition of (13).



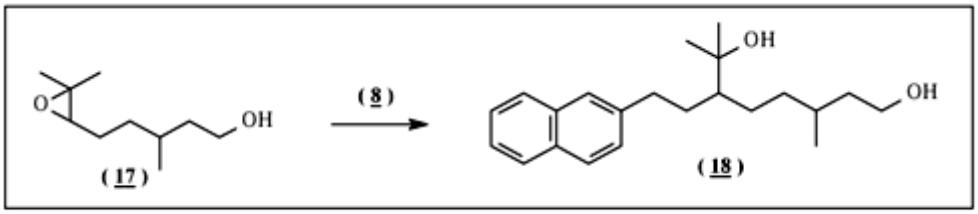
SCHEME 2

After the failure of the direct alkylation strategy, we examined the stepwise introduction of the 2-naphthylethyl group *(scheme 3)*. a-Methylenation of (10) to (14) followed by conjugate addition of an organomettalic reagent seemed a promising alternative. However, literature procedures via hydroxymethylation [4] or hiomethylation [9] described for c- and d-lactones produced only decomposition of the e-lactone. Another possibility was the preparation of the aldehyde-lactone (16). Subsequent Grignard reaction should then introduce the 2-naphthyl moiety and catalytic hydrogenation would lead to an intermediate of type (4). Indeed, (10) was successfully allylated to (15) and then cleaved to (16), as evidenced by spectroscopic means, but the latter decomposed during the work up procedure. Summarizing the different variants of the alkylation strategy, we can conclude that a cationic 2-naphthylethyl synthon is not suitable for substitution reactions in basic as well in Lewis acid catalyzed conditions. Furthermore, e-lactones proved to be unstable when stepwise introduction of the substituted was tried.



SCHEME 3

In consequence, our attention moved to the second main strategy of *scheme 1*. Because of the unattractive preparation of the unsaturated alcohol (9) described in the literature,[13] once more a model compound was used for explorative work. Racemic citronellol, which differs from (9) by one carbon atom more in the chain and by the position of the methyl group, was transformed to the known epoxide (17) .[6] Reaction with an excess of the cuprate (8), prepared from (7) (X = I), produced the crystalline diol (18), probably as a mixture of diastereomers *(scheme 4)*. The only side product was 1,4-di-2-naphthylbutane [5] formed by thermal dimerization of the cuprate (8).



SCHEME 4

CONCLUSION

The successful coupling reaction *(scheme 4)* demonstrates that the carbanionic 2-naphthylethyl synthon is more suitable for C-C bond formation than the cationic one. It opens now the possibility to obtain the key-intermediate (3) by an analogous reaction.

The development of a practical synthesis of the unsaturated alcohol (9) as a pure enantiomer and its use in the asymmetric synthesis of *cordiaquinone A* is now in progress.

ACKNOWLEDGEMENTS

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BATALINI, C., BIEBER, L.W. Estudos Modelo da Síntese do Meroterpenóide Natural cordiaquinona A. *Ecl. Quím.* (São Paulo), v.26, p. ,2001.

RESUMO: Duas estratégias principais visando a síntese do meroterpenóide natural *cordiaquinona A* (1) – isolada das raízes de *Cordia corymbosa* G. Don (Boraginaceae) – foram testadas em compostos modelo. Enquanto todas as variantes envolvendo a alquilação de e-caprolactona (10) falharam, o acoplamento de epoxicitronelol (17) com um organocuprato apropriado ocorreu no sentido esperado.
PALAVRAS-CHAVE: Naftoquinona meroterpenóide, *Cordia corymbosa*, Boraginaceae e-caprolactona, epoxicitronelol, organocuprato.

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