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Synthesis of a 5-Deoxypyranoanthracycline : an Entry Into Novel Analogs of Idarubicin

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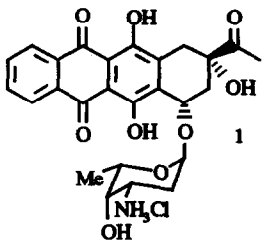
Abstract: *This paper describes a convergent and regioselective synthesis of 5-deoxypyranoanthracycline 2 using pyranoquinone 12 which is a versatile intermediate for the synthesis of this new class of heteroanthracyclines.*

Deoxyanthracyclines[1] and heteroanthracyclines[2] are two important classes of anthracycline analogs that have shown some interesting properties as antitumor agents. We recently disclosed novel pyranyl-anthracycline analogs[3,4] of Idarubicin (1),[5] related to 2 and 3 which have good *in vitro* antitumor activity. These results prompted us to develop an efficient synthesis of this class of compounds.



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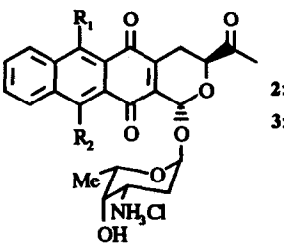
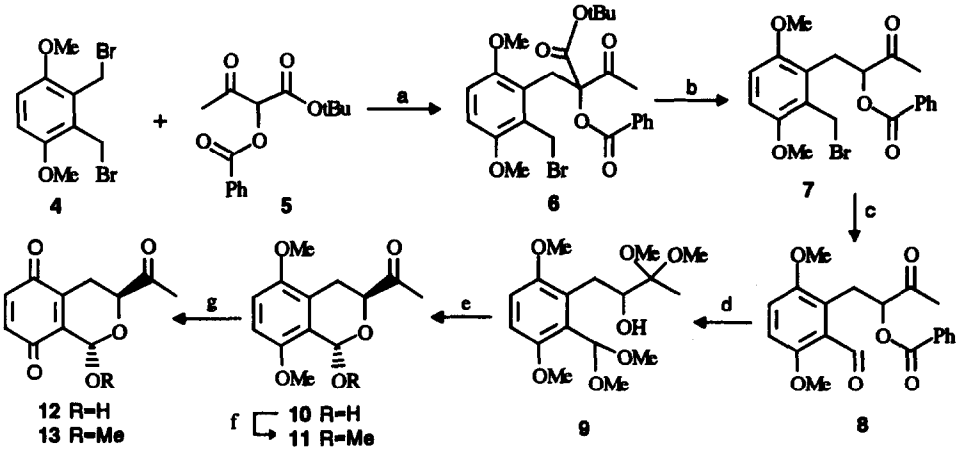


2: R_1=OH, R_2=H
3: R_1=H, R_2=OH

Retrosynthetic analysis showed that pyranoquinone **12** (Scheme 1) was an ideal key intermediate for this synthesis. Since **12** could serve as a precursor for many analogs in this series, its synthesis has to be easily amenable to multigram scale. The starting material that we have chosen for this purpose is the known dibromo compound **4**, obtained in 2 steps from 2,3-dimethyl- hydroquinone.[6] Inspired by Lawesson's methodology for the preparation of acyloins,[7] we decided to use β-ketoester **5**[8] for the introduction of the α'-alkoxy methyl ketone moiety. Thus, treatment of **4** with this β-ketoester under basic conditions (K_2CO_3, DMF:THF, 60°C; or Cs_2CO_3, THF:CH_3CN, r.t.) produced alkylated compound **6**[9] in high yield (80-85%). Because of the steric hindrance created by the bulky β-ketoester moiety in **6**, the reactivity of the second benzylic bromide is highly diminished and, therefore, the disubstituted compound is found only in trace amounts. Treatment of **6** with *p*-toluenesulfonic acid in refluxing benzene[7] produced **7** together with a few side products. However, decarboalkoxylation with 48% HBr in acetone at 45°C afforded **7** exclusively in very high yield (90-95%). Oxidation of the latter with dimethyl sulfoxide in the presence of sodium bicarbonate at 90°C[10] gave only a moderate yield (50-60%) of aldehyde **8**. Both silver carbonate and silver fluoride gave **8** in higher yields, although silver tetrafluoroborate[11] and several alternative reagents[12] failed to improve the yield. The best results were obtained with 3 eq. of silver carbonate in dimethylsulfoxide at 90°C which afforded aldehyde **8** in 78% yield after flash chromatography. In order to obtain clean debenzoylation, both carbonyls have to be protected as acetals, ($HC(OMe)_3$, PPTS, MeOH, r.t.). The benzoate group was cleaved by adding a 1N solution of sodium hydroxide to the reaction mixture and

refluxing it for 5 hours. After work up, the crude alcohol **9** was treated twice[13] with *p*-toluenesulfonic acid in acetone and water to give isochroman **10**[14] in over 80% yield from **8**.



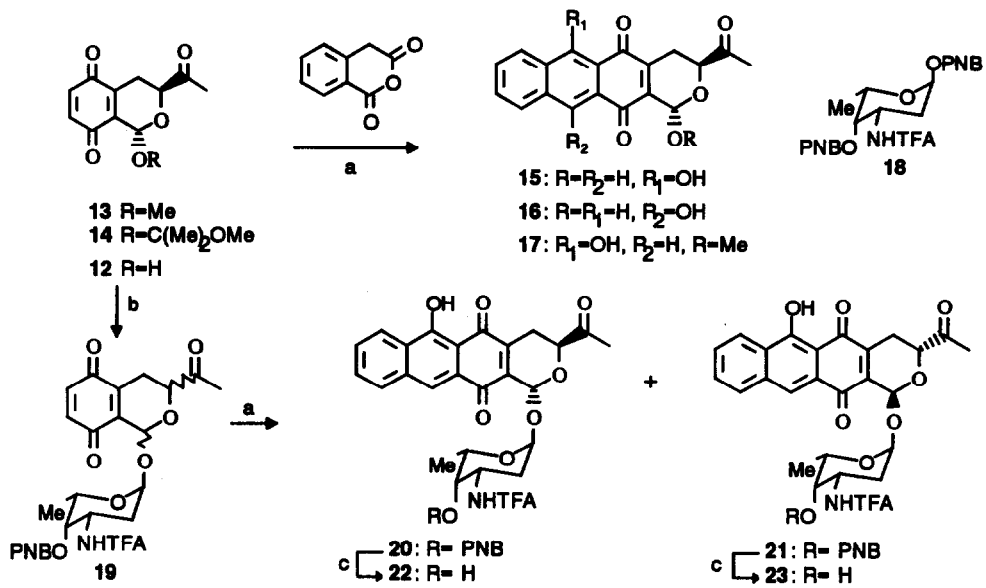
Scheme 1

a. K_2CO_3, DMF:THF (1:2), 60°C; or Cs_2CO_3, THF:CH_3CN (1:2), r.t. (80-85%). b. HBr 48%, acetone, 45°C (90-95%). c. Ag_2CO_3, DMSO, 90°C (75-80%). d. $HC(OMe)_3$, PTSA, MeOH, r.t.; then NaOH (1N), reflux. e. PTSA, Acetone:water (>80% from **8**). f. $HC(OMe)_3$, PPTS, MeOH, r.t. (100%). g. Ceric ammonium nitrate, $NaHCO_3$, CH_3CN:H_2O, -5°C (85-90%).

Methoxy isochroman **11** was obtained by a brief treatment of **10** with trimethyl orthoformate and pyridinium *p*-toluenesulfonate in methanol. The absence of homobenzylic long range coupling in PMR of **10** and **11** indicates a trans stereochemical arrangement.[15] The oxidation of isochromans **10** and **11** with CAN (ceric ammonium nitrate, $NaHCO_3$, CH_3CN:H_2O,-5°C)[16] afforded pyranoquinones **12** and **13** respectively (85-90%). The synthesis of **12** has been realized in 6 steps and 45% overall yield from **4**.[17] All products, including starting materials, are solids and can be recrystallized. This sequence has been carried out on multigram scale without any problem.

Treatment of quinone **12** (Scheme 2) with the lithium enolate of homophthalic anhydride[18] produced an inseparable mixture of **15** and **16** in a 2:1 ratio. However, **13** led to regioisomer **17** in 55% yield with high regiochemical control (≥95%).[19] Because of the electron-poor quinone system, which prevents formation of the requisite cyclic oxonium ion, acetal **17** could not be easily hydrolysed to lactol **15**. We were able to solve this problem with the use of a more labile protecting group. Treatment of quinone **12** with methoxypropene and pyridinium *p*-toluenesulfonate in ether/tetrahydrofuran mixture produced **14** in quantitative yield. Treated of **14** according to Tamura's methodology[18] afforded, after hydrolysis and crystalization deoxyanthraquinone **15** in 64% yield. Regiochemical assignment was secured by a long range HETCOR NMR experiment. Condensation of **15** with suitably protected L-daunosamine (**18**) was attempted under the conditions developed by Terashima *et al.*[20] using trimethylsilyl trifluoromethanesulfonate and activated 4Å molecular sieves powder in a dichloromethane/ether mixture at -15°C. This reaction produced **20** and **21** in quite low yield, mainly because of the very low solubility of **15** in dichloromethane. This last synthetic problem was solved by carrying out the glycosidation reaction on pyranoquinone **12** to give **19** as a

diastereoisomeric mixture. Interestingly, the quinone system was very stable under the reaction conditions and after 4 hours **19** seems to be the only product formed. Treatment of crude **19** with homophthalic anhydride enolate from -78°C to room temperature produced a 1:1 mixture of **20** and **21** in 35-40% overall yield from **12** and the products were separated by flash chromatography (toluene-acetone 95:5). The *p*-nitrobenzoate was cleaved with sodium methoxide in methanol at 0°C affording **22** or **23** in high yield (90-100%) in both cases.[21] Compound **2** and its diastereoisomer were both obtained in 30-35% yield by treatment of **22** and **23** with a dilute aqueous basic solution, followed by an acidic work-up.



Scheme 2

a. LDA, Homophthalic anhydride, THF/Et_2O, -78°C to r.t.. b. TMSOTf, di-O-*p*-nitrobenzoyl N-trifluoroacetyl daunosamine (**18**), CH_2Cl_2:Et_2O, -15°C. c. NaOMe, MeOH, 0°C (90-100%).

In conclusion, we have reported an efficient synthesis of pyranoquinone **12** and a convergent strategy for the synthesis of a new family of heteroanthracyclines. The synthesis of regioisomer **3** is presently under investigation. The biological evaluation of these compounds will be published elsewhere.

Acknowledgments We would like to thank Dr. K. T. Nwe at McGill University for her help in recording CD curves, Drs. S. Noble and M. Lichty from Glaxo Inc., and Drs J. W. Gillard and G. Dionne from Biochem Thérapeutique Inc., for useful discussions and support. We would also like to thank the Government of Quebec for financial support in the form of an Industrial Research Fellowship to J.-F.L..

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8. β-Ketoester **5** was prepared using 5 eq. of t-butylacetoacetate, 5 eq. of sodium hydride and 1 eq. of benzoyl peroxide in benzene (60% yield after crystallization, mp: 65-66°C.).
9. All spectra (^1H, ^{13}C NMR and/or HRMS, and IR) are in agreement with the assigned structures.
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13. After one treatment, a mixture of **10** and **11** was obtained.
14. **10**: mp: 136-138°C; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.73 (d, 1H, J= 9.0 Hz), 6.71 (d, 1H, J= 9.0 Hz), 6.22 (d, 1H, J= 3.4 Hz), 4.70 (dd, 1H, J= 4.1, 12.4 Hz), 3.82 and 3.77 (2s, 6H), 3.06 (dd, 1H, J= 4.1, 17.5 Hz), 2.97 (d, 1H, J= 3.4 Hz), 2.51 (dd, 1H, J= 12.4, 17.5 Hz), 2.32 (s, 3H); HRMS m/e Calcd: 252.0998, Found: 252.0976. A review on the synthesis of isochromans has recently been published : Markaryan, E. A., Samodurova, A. G., *Russian Chem. Rev.*, **1989**, 58, 479.
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16. Sodium bicarbonate (1.8 eq) was used to partially neutralize the acidity of the reagent and avoid the formation of **13** from **10**. See Baciocchi, E., Casu, A., Ruzziconi, R., *Tetrahedron Lett.*, **1989**, 30, 3707, for the use of $NaHCO_3$ with CAN.
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21. The absolute stereochemical assignment of these diastereoisomers is based on the CD curves. **22**: mp: 207-210°C; ^1H NMR ($CDCl_3$, 300 MHz): δ 13.71 (s,1H), 8.40 (m, 1H), 7.98 (s, 1H), 7.85 (m, 1H), 7.65 (m, 2H), 6.78 (d,1H, J=8.1 Hz), 5.94 (s,1H), 5.58 (d, 1H, J=2.5 Hz), 4.53 (dd, 1H, J= 3.8,11.6 Hz), 4.33 (m, 1H), 4.14 (q, 1H, J=6.5 Hz), 3.63 (broad s, 1H), 3.09 (dd, 1H, J= 3.8, 19.5 Hz), 2.50 (dd, 1H, J= 11.6, 19.5 Hz), 2.33 (s, 3H), 2.10 (m, 3H), 1.27 (d, 3H, J= 6.5 Hz); HRMS m/e (M^++Na) Calcd: 586.1314, Found: 586.1301.

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