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Tandem Reduction / Intramolecular Hydroxyalkylation of (3-Hydroxyphenyl)alkanoates: a New Regioselective Approach to 1,8-Dihydroxytetralins

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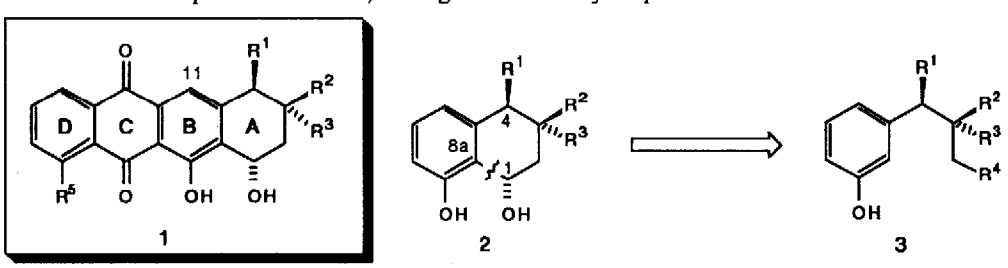
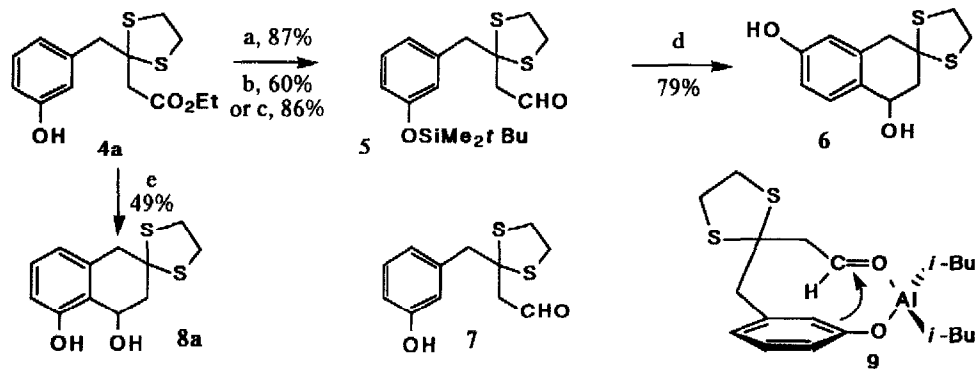
Abstract: 4-(3-hydroxyphenyl)-butanoates **4**, on treatment with DIBALH, followed by hydrolytic work-up, undergo a novel completely regioselective intramolecular hydroxyalkylation reaction to give 1,8-dihydroxytetralins. The yield of the reaction depends heavily on the structure of starting material, best results being achieved with 3,3-disubstituted butanoates.

The discovery that 11-deoxyanthracyclinones **1** are present as aglycone portions in some antibiotics possessing significant anti-cancer activity and reduced cardiotoxicity has attracted the interest of several research groups, stimulating extensive synthetic work in this field.[1] A possible strategy for the preparation of these linearly fused units involves first the assemblage of the AB ring system followed by its coupling with the remaining CD rings to complete the tetracyclic arrangement. Various different disconnections can be envisaged for the AB fragment, and some elegant syntheses had already been published.[2] In the course of a research program directed to the development of new synthetic routes to this class of antibiotics, we planned to prepare the 1,8-dihydroxytetralin fragment **2** through a completely new approach, based on an intramolecular C-C bond formation between the positions 1 and 8a, starting from a monocyclic precursor **3**.



In order to examine the the feasibility of this project, we decided to synthesize some suitably substituted 4-(3-hydroxyphenyl)butanals, and to study in details the factors controlling the *ortho -para* ratio in the intramolecular hydroxyalkylation. For this purpose the model "meta" ester **4a**[3] was first prepared, planning to accomplish its conversion into the corresponding phenolic aldehyde **7** either *via* a protection-reduction-deprotection sequence, or through direct reduction (Scheme 1).[4] Thus **4a** was first protected as the dimethyl-t-butylsilyl ether and then converted into silylated aldehyde **5** either through direct chemoselective reduction with DIBALH, or *via* a two-step sequence (reduction to the primary alcohol followed by Swern oxidation). Further treatment with ethanolic NaOH removed the protecting group[5] and the resulting phenolic aldehyde **7** immediately cyclized, under these basic conditions, to give in good yield exclusively the 1,6-dihydroxytetralin **6**, deriving from attack of the carbonyl group at the *para* position of the aromatic ring. On the other hand, when the reduction with DIBALH was carried out directly on the unprotected ester **4a**, the main product turned out to be, instead than

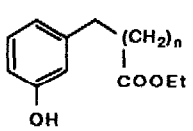
Scheme 1



a) Me_2t-BuSiCl, imidazole, DMF, r.t.; b) DIBALH, CH_2Cl_2, -78° c) 1. $LiBH_4$, Et_2O; 2. $(COCl)_2$, DMSO, Et_3N, -78° → -40°C; d) NaOH, MeOH, r.t.; e) see typical procedure in the Table.

the expected aldehyde **7**, an alcohol whose structure, determined by ^1H and ^{13}C NMR, corresponded to the 1,8-dihydroxytetralin **8a**, as confirmed by its conversion into iso-propylidene derivative **11a** (see Table). This result was particularly interesting, since one-pot transformation of the starting phenolic ester **4a** into **8a**, through a tandem reduction-cyclization reaction, was realized. Moreover the reaction proceeded with complete *ortho* regioselectivity (no *para* compound **6** was detected) and in satisfactory yield (49%), which was further improved by *in situ* derivatization of **8a** to give the diacetate **10a** (75% yield from non-recovered **4a**).[7] This outcome demonstrated the possibility of performing C-C bond formation between position 1 and 8a, thus opening a new synthetic route to fragment **2a**.

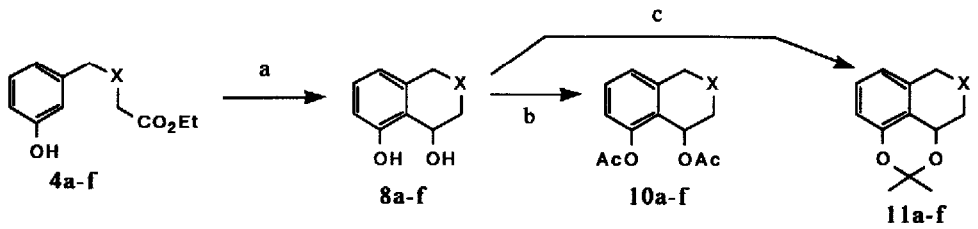
In order to define the scope and limitations of this unprecedented reaction, we synthesized a series 4-(3-hydroxyphenyl)butanoates **4b-f**, variously substituted at position 3 of the aliphatic chain,[3] as well as ethyl 3-(3-hydroxyphenyl)propanoate **12** and 5-(3-hydroxyphenyl)pentanoate **13**,[3] and subjected them to the same reaction conditions already employed for **4a**. To our surprise we noted big differences in their behaviour. Actually the yield and the product distribution appeared to depend dramatically upon the length of carbon chain as well as on the presence of substituents (at the moment we examined only the effect of modifications at position 3). First of all we observed that compounds **12** and **13** did not furnish at all respectively the five and seven-membered cyclization compounds, leading instead in good yield to the corresponding aldehydes deriving from simple reduction. On the other hand, compounds **4c** and **4d**, which bear no substituents at position 3, afforded **8c** and **8d** only in low yields, due to the formation of several by-products.[7] It should be noted that in this case, like for **4a**, very little or no aldehyde was detected. On the contrary, good yields were obtained starting from dithiane **4b** and 3,3-dimethyl derivative **4f**, which are both disubstituted at position 3, while the behaviour of monosubstituted **4e** falls in between. Thus, although further data may be desirable in order to draw generalization, it seems that the presence of a double substitution at position 3 is crucial for the achievement of satisfactory yields.[8]



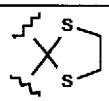
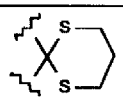
12 : n=1
13 : n=3

Finally, about the mechanism and the factors responsible for the observed highly regioselective cyclization, at the moment we are only able to advance a tentative explanation. Addition at -78°C of 2 eq. DIBALH to the phenolic esters **4** may generate initially a diisobutylaluminium phenolate and then effects ester reduction to give an [illegible] (saturated NH_4Cl) then frees the aldehyde group, which adds to the aromatic ring under the intramolecular catalysis given by the aluminium phenolate. The intervention of chelated transition state **9** (Scheme 1) can explain the preferential formation of *ortho* cyclization products **8**.[10] On the contrary, when the intramolecular hydroxyalky-

Table: Intramolecular Cyclization of Esters 4a-h[a]



a) 1) DIBALH, CH_2Cl_2; 2) NH_4Cl b) Ac_2O, CH_2Cl_2, DMAP, r.t., 2h c) 2-methoxypropene, TsOH, CH_2Cl_2, 0°C, 15 min

Entry	Starting ester	X	Yield of 8[b]	Yield of 10[c] (from 4)	Yield of 11 (from 4)
1	4a		42% (49%)	54% (75%)	40%
2	4b		32%	40% (54%)	40%
3	4c	$-CH_2-$	10% (13%)	10% (18%)	2%
4	4d	-O-	8%	not det.	not det.
5	4e	$-CH(CH_3)-$	not det.	38% (52%)[d]	8%
6	4f	$-C(CH_3)_2-$	65% (69%)	60% (64%)	55%

a) Typical procedure: A solution of **4** (1.0 mmol) in dry CH_2Cl_2 (10 ml) was cooled to -78°C and treated with DIBALH (1N in CH_2Cl_2) (2.1 mmol). After 15 min, the mixture was quenched with saturated aqueous NH_4Cl (15 ml), warmed to r.t. and stirred for 5h. After dilution with saturated aqueous Na,K tartrate (25 ml), and Et_2O (30 ml), the mixture was stirred for 30 min. Separation of the phases (in some cases filtration through a celite pad was necessary to remove emulsions) and evaporation afforded crude **8**, which was purified through chromatography or *in situ* derivatized to give **10** or **11**. b) Yield from non-recovered **4** are in brackets. c) Yield from non-recovered O-acetylated **4** in brackets. d) **10e** was obtained as an approximately 1:1 diastereomeric mixture.

lation is carried out under basic conditions and in the absence of a metal atom capable to promote chelation, the *para* position seems to be favoured, most likely for steric reasons, affording 1,6-dihydroxytetralin **6**.

Since the dithiolane and dithiane rings are readily removable protecting groups, which can furnish the corresponding carbonyl compounds, the 1,8-dihydroxytetralins **8a** and **8b** represent versatile intermediates that may find useful applications in the chemistry of 11-deoxyanthracyclinones. Work in this field is under development in our laboratory.

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3. Esters **4a-f**, **12** and **13** are all new compounds and their preparation was in some cases not trivial Synthesis of the esters **4a-c** (starting from commercially available 3-hydroxyphenylacetic acid) : **4a** and **4b**: a) MOMCl, Et_3N, CH_3CN, reflux; b) KOH/MeOH 9:1, r.t., 30'; c) 1) CDI, CH_3CN, 30'; 2) magnesium enolate of $EtO_2C\text{-}CH_2CO_2H$, THF, 60°C, overnight, 54% (3 steps); d) $HS(CH_2)_nSH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, r.t., 80% (**4a**), 76% (**4b**); **4c**: a) H_2SO_4, abs. EtOH, reflux, 24 h; b) BzlBr, K_2CO_3, DMF, 88% (2 steps); c) 1 eq DIBALH, CH_2Cl_2, -78°C; d) $Ph_3P{=}CH\text{-}CO_2Et$, CH_2Cl_2, r.t., powdered 4 Å molecular sieves, 3 h, 84%; e) H_2, PtO_2, Pd/C, EtOH, r.t., 24 h, 96%. **4e** : a) see a) and b) in preparation of **4c**; b) KOH, MeOH/H_2O 9:1, r.t., 6 h, 91%; c) MeONHMe·HCl, WSC, H_2O/THF 4:1, r.t., 2.5 h, 94%; d) MeLi, THF, -60°C, 1.25 h, 85%; e) $Me_3SiCH_2CO_2Et$, lithium dicyclohexylamide, THF, -78° → -50°C, 2 h, 87%; f) H_2, PtO_2, Pd/C, EtOH, r.t., 5.5 h, 88%. Synthesis of esters **4f**, **12**, and **13** starting from commercially available 3-hydroxybenzaldehyde) : **12**: a) malonic acid, pyridine, piperidine, reflux, 8 h, 93%; b) abs. EtOH, H_2SO_4, reflux, 7 h, 97%; c) H_2, PtO_2, EtOH, r.t., 20 h, 98%. **13**: (starting from **12**): a) BzlBr, K_2CO_3, DMF, 80°C, 24 h, 91%; b) 1) 1 eq DIBALH, CH_2Cl_2, -78°C, 30'; 2) $Ph_3P{=}CH\text{-}CO_2Et$, CH_2Cl_2, powdered 4 Å mol. sieves, 2.5 h, r.t., 61% (2 steps); c) H_2, PtO_2, Pd/C, EtOH, r.t., 24 h, 96%. **4f**: a) see a) and b) in preparation of **12**; b) 1) LDA, HMPA, MeI, THF, -78°C, 45'; 2) LDA, HMPA, MeI, -78°C, 15', 47%; c) DIBALH (2 equiv.), CH_2Cl_2, -65° → -40°C, 5.5 h, 86% or $LiBH_4$, Et_2O, t. amb., 24 h, 93%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -75° → -30°C; e) 2-lithium-2-trimethylsilyl-1,3-dithiane, THF, 0° → 25°C, 81% (2 steps); f) $HgCl_2$, abs.EtOH, r.t., 1 h, 79% ; g) $BF_3{\cdot}$ Et_2O, EtSH, t. amb., 2 h, 88%. Synthesis of ester **4e** starting from commercially available 3-hydroxybenzyl alcohol : a) BzlBr, K_2CO_3, DMF, 70°C, 6 h, 75%; b) $BrCH_2CO_2t$-Bu, NaOH 50%, benzene, $Bu_4N^+HSO_4^-$, r.t., overnight, 73%; c) abs. EtOH, H_2SO_4, reflux, 2 h; d) H_2, Pd/C, EtOH, r.t., 1.5 h, 83% (2 steps).
4. Preliminary attempts to effect the cyclization at the ester stage failed.
5. Desilylation of **5** with n-$Bu_4NF{\cdot}3\ H_2O$ in THF afforded aldehyde **7** in only poor yield due to extensive decomposition. Formation of **6** or **8a** was not observed under these conditions.
6. The substrate selectivity of DIBALH in the reaction herein studied is never total, and so the cyclization products are always accompanied by variable amounts of unreacted **4** as well as of the primary alcohol deriving from further reduction of the aldehyde.
7. Compounds **5c**, **5d**, and, although to a lesser extent, **5e** were found to be somewhat unstable under the reaction conditions as well as during purification or derivatization, expecially in the presence of acids. See for example the very low yield of iso -propylidene derivatives **7c** and **7e**. On the contrary **4a**, **4b**, and **4f** seem do be definitely more stable. Thence the low yields of entries 3-4 may be due to relatively fast decomposition of **5c** and **5d** in the reaction conditions.
8. A tentative explanation of this phenomenon will be reported in a forthcoming full paper.
9. By quenching the reaction mixture with methanolic $NaBH_4$, instead of NH_4Cl, only the primary alcohol deriving from further aldehyde reduction was obtained, together with some unreacted **4**, while no cyclization product **5** was observed. On the other hand, by using more acidic (i.e. AcOH) aqueous quenching conditions, the yield dropped significantly. Finally lower yields were obtained when the aluminium salts were removed soon after quenching with aqueous NH_4Cl. These results strongly suggest that cyclization occurs only after aqueous quenching.
10. *Ortho*-directed intermolecular acylations and hydroxyalkylations of phenols, which take advantage of the formation of a six-membered cyclic transition state deriving from covalent bonding of the Lewis acidic catalyst with the phenolic hydroxyl, have been extensively studied in recent years.[11]
11. Casnati, G.; Casiraghi, G.; Pochini, A.; Sartori, G.; Ungaro, R. *Pure Appl. Chem.* , **1983**, 55 , 1677; Sartori, G.; Casnati, G.; Bigi, F.; Predieri, G. *J. Org. Chem.*, **1990**, 55 , 4371-4377 and references therein.

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