Tetrahedron Letters, Vol. 34, No. 52, pp. 8549-8552, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Chemoenzymatic Approach to the AB Ring System of Aklavinone

Giuseppe Guanti,* Luca Banfi, Stefano Brusco, and Renata Riva

Istituto di Chimica Organica dell'Università degli Studi di Genova, e C.N.R., Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici, corso Europa 26, I-16132 GENOVA (Italy)

Abstract: Both enantiomers of compound **3**, a possible intermediate for the AB ring system **2** of Aklavinone **1**, were obtained in optically active form from diol **7**. Key steps were the preparation of both enantiomers of monoacetate **8d**, *via* enzymatic reactions that utilize PPL as catalyst, and the construction of ring A in a totally regioselective manner.

We have recently described a new completely regioselective intramolecular hydroxyalkylation reaction of phenols, which allows the preparation of 1,8-dihydroxytetralins starting from 4-(3-hydroxyphenyl)butanoates.[1] In the course of our program on the synthesis of new antitumoral agents in the field of tetracyclines, we envisaged the possibility of using this novel strategy for assembling the AB ring system of Aklavinone **1**. This compound, which is the aglycone of Aclacinomycin A, an antibiotic with a significant anti-cancer activity accompanied by low cardiotoxicity, was the target of many synthetic works in the last years.[2] Our retrosynthetic analysis is showed in Scheme 1: we selected the ester **4** as the key intermediate to be submitted to the cyclization reaction and the monoprotected diols **5** as the chiral precursors. For this purpose we prepared, by a chemoenzymatic procedure (that is PPL catalyzed monohydrolysis of diacetates **6a-d** and PPL catalyzed monoacetylation of diol **7**), a series of optically active monoacetates **8a-d**, differently protected at the phenolic hydroxy group, with the aim to convert them, by protecting group exchange reactions, into both enantiomers of various compounds of general formula **5**.

Scheme 1

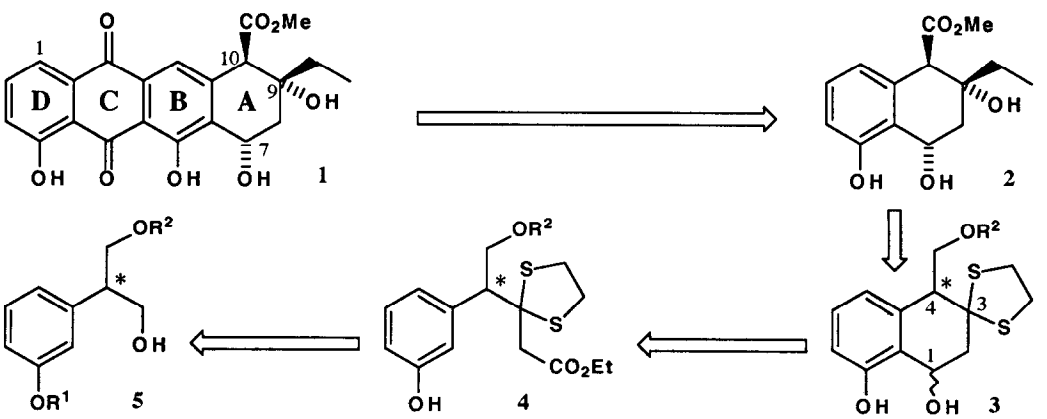
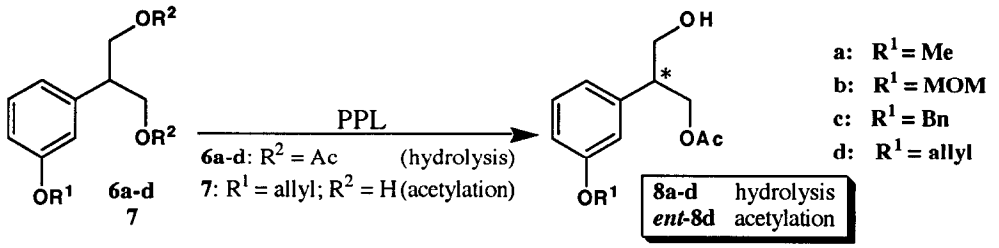


Table: preparation of PPL catalyzed 3-acetoxy-2-(3-alkoxyphenyl)-1-propanols



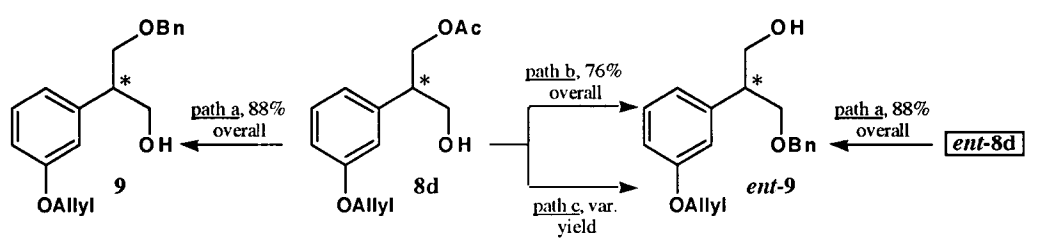
Entry	R^1	Reaction	Solvent	Reaction time	Conversion	Yield	E.e.[a]	$[\alpha]_D$
1	Me	hydrolysis	H_2O/*i*-Pr_2O 85 : 15	48 h	51%	57%	93%	n.d.
2	MOM	hydrolysis	H_2O/*i*-Pr_2O 85 : 15	51.2 h	55%	46%	50%	n.d.
3	Bn	hydrolysis	H_2O/*t*-BuOH 75 : 25	47 h	46%	43%	96%	-11.4°
4	allyl	hydrolysis[b]	H_2O/*i*-Pr_2O 83.7 : 16.3	24.5 h	60%	66%	95%	-12.0°
5	allyl	acetylation[c]	vinyl acetate	24 h	47%	69%	90%	+11.5°

Note: a) determined by ^{1}H-n.m.r. in the presence of Eu(hfc)$_3$; b) 8.4 ml solvent/mmole diacetate; 310 mg crude PPL [from Sigma (13.1 U/mg)]/mmole diacetate, 20°C; c) 18.0 ml vinyl acetate/mmole diol; 1041 mg supported PPL (corresponding to 231 mg of crude PPL)/mmole diol, 1 mg powdered 3Å molecular sieves/ml solvent, 0°C (according to Ref. 6).

On the basis of the results of enzymatic asymmetrization (see Table) and of preliminary studies performed on racemic templates,[3] we chose allyl and benzyl as protecting groups for the phenolic and the hydroxyalkyl groups respectively. The two enantiomers of **9** were prepared either starting from the same monoacetate **8d**,[4,5] following two different routes (path a and b in Scheme 2) or independently starting from the two enantiomers **8d** and ***ent*-8d** (see Table, entry 4, 5) and following the same more efficient path a.[7]

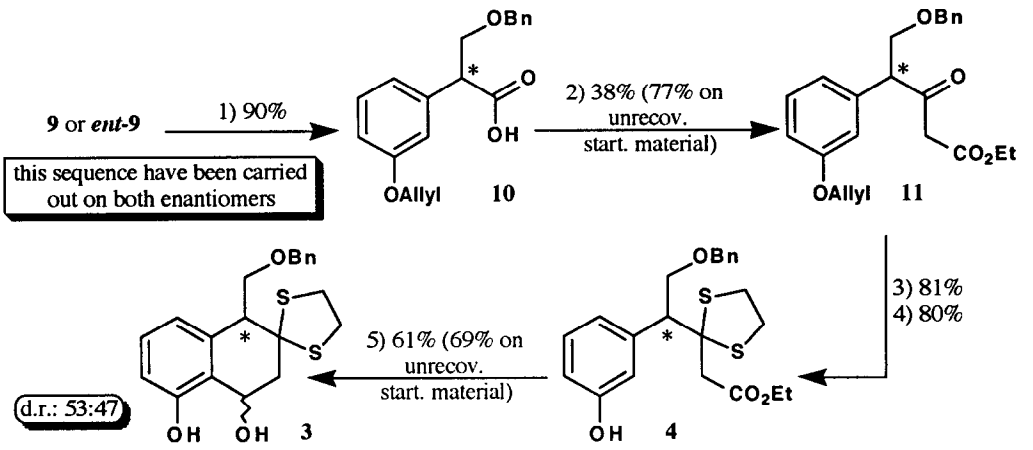
The transformation of **9** or ***ent*-9** into the 1,8-dihydroxytetralin **3** is illustrated in Scheme 3. The oxidation of the primary alcoholic function to carboxylic acid **10** has been realized using Jones reagent without racemization.[8] The homologation reaction was the most critical step of the whole process. After many attempts under different conditions the elongation was realized using the lithium enolate of ethyl acetate and the acid **10**, activated as the imidazolide.[9] These conditions represent at the moment the best compromise between

Scheme 2



Path a: 1) i. dihydropyran, *p*-TSA, CH_2Cl_2, r. t.; ii. KOH, MeOH, r. t., 97%; 2) BnBr, NaH, DMF, r. t., 98%; 3) MeOH, *p*-TSA, r. t., 93%. Path b: 1) i. $Ph_2tBuSiCl$, imidazole, DMF, r. t.; ii. KOH, MeOH, r. t., 91%; 2) i. dihydropyran, *p*-TSA, CH_2Cl_2, r. t.; ii. *n*-$Bu_4N^+F^-$, THF, r. t., 92%; 3) BnBr, NaH, DMF, r. t., 98%; 4) MeOH, *p*-TSA, r. t., 93%. Path c: see Note 7.

Scheme 3



1) Jones oxidation, acetone, 0°C; 2) i. CDI, THF, r. t.; ii. CH_2=C(OLi)OEt, -78°C; 3) Bu_3SnH, AcOH, $Pd(PPh_3)_4$, toluene, r. t.; 4) i. ethanedithiol, TMSOTf, CH_2Cl_2/THF, 4Å molecular sieves; ii. addition of **10** to substrate, r. t.; 5) i. 2 eq of DIBALH, CH_2Cl_2, -78°C, 15' ii. NH_4Cl, then r. t., 6 h.

racemization and chemical yield.[10]

The transformation of **11** into **4** was not trivial: the carbonyl group had to be protected and the allyl group had to be removed before the cyclization reaction. We obtained best results, in terms of reactivity and chemical yield, when the phenol was liberated first; among the methods reported for mild deallylation, Bu_3SnH in the presence of Pd(0) as catalysts gave optimal results.[11]

With regard to the carbonyl group, the protection of choice for the continuation of the synthesis was found to be the dithiolane. However, also this step was troublesome. Classical conditions (ethanedithiol, $BF_3{\cdot}Et_2O$) led especially to fast benzyl group cleavage.[12] The resulting hydroxy ester rapidly cyclizes to give the six membered lactone as soon as the carbonyl group is protected. This lactone could not be transformed into useful intermediates for our synthesis. After many attempts, we finally solved this problem by employing an original methodology: ethanedithiol was bis silylated by *in situ* treatment with trimethylsilyl triflate (without added base), followed by addition of **11**. Under these conditions, thioketalization took place in good yields without affecting the benzyl ether.[13]

As the last step we transformed **4** into **3**, following the protocol of cyclization recently described by us for 4-(3-hydroxyphenyl)butanoates;[1] indeed, treatment of the ester **4** with 2 eq of DIBALH, followed by quenching with aqueous NH_4Cl, furnished **3** in good overall yield (69%).[10a] As previously noticed,[1] the presence of a tetrasubstituted carbon in position 3 was crucial for suppressing side reactions. As expected, the diastereoselectivity in the formation of a new chiral centre in 1 is very low (53 : 47), probably due to the distance of the pre-existent chiral centre from reaction site. This is not a real problem in view of the synthesis of Aklavinone: actually, as previously reported,[2a] the stereochemistry of carbon 7 (1 in compound **2**) can be modified in the last step of the reactions sequence, introducing the hydroxy group exclusively in the α position.

In conclusion, we have shown how, starting from some new chiral building blocks, obtained by a chemoenzymatic methodology, and taking advantage of the regioselective cyclization of 4-(3-hydroxyphenyl) butanoates, the synthesis of protected 1,8-dihydroxy-4-hydroxyalkyl-3-oxo-tetralins is feasible. Researches for transforming these intermediates into the AB ring system of Aklavinone are in progress in our laboratories.

We wish to thank Miss Silvia De Vito for her precious collaboration and CNR (Progetto Finalizzato Chimica Fine) and M.U.R.S.T. for financial assistance.

REFERENCES AND NOTES

1. Guanti, G.; Banfi, L.; Narisano, E.; Riva, R.; Thea, S. *Tetrahedron Lett.* **1992**, *33*, 3919-3922.
2. Enantioselective syntheses of **1**: **a**) McNamara, J. M.; Kishi, Y. *Tetrahedron* **1984**, *40*, 4685-4691 **b**) Rizzi, J. P., Kende, A. S. *Tetrahedron* **1984**, *40*, 4693-4700; enantioselective syntheses of AB ring fragment: **c**) Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592-4597; **d**) Davis, F. A.; Kumar, A. *Tetrahedron Lett.* **1991**, *32*, 7671-7674.
3. These results will be reported in a forthcoming full paper.
4. Preparation of **8d** from 3-hydroxyphenyl acetic acid: **a**) EtOH, H_2SO_4, reflux, overnight, 94%; **b**) allyl bromide, K_2CO_3, 55°C, 4 h, 96%; **c**) α) LDA, THF, -78°C; β) $ClCO_2Et$, -78°C, 30', 90%; **d**) DIBALH, CH_2Cl_2, 0°C → r. t.; 63%; **e**) Ac_2O, pyridine, r. t., 3 h, 96%; **f**) see Table.
5. The absolute configuration of **8d** and ***ent*-8d** is only guessed; according with *para* substituted analogues, for which PPL catalyzed hydrolysis always gives *S* monoacetates (Guanti, G.; Narisano, E.; Podgorski, T.; Thea, S.; Williams, A. *Tetrahedron* **1990**, *46*, 7081-7092), also in this case we expected **8d** to be *S* and ***ent*-8d** to be *R*. In this hypothesis, for Aklavinone synthesis, ***ent*-8d** should be used.
6. Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron: Asymm.*, submitted for publication.
7. Path c, that is the direct benzylation of **8d** was not satisfactory, since classical conditions (benzyl bromide, NaH) (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis* **1991**, John Wiley & Sons, New York) provoked total racemization; using Ag_2O as base (Gargiulo, D.; Blizzard, T. A.; Nakanishi, K. *Tetrahedron* **1989**, *45*, 5423-5432) the racemization was about 30%, while under acidic conditions (benzyl trichloroacetimidate, TfOH) (Eckenberg, P., Groth, U.; Huhn, T.; Richter, N.; Schmeck, C. *Tetrahedron* **1993**, *49*, 1619-1624) the reaction was troublesome, giving unreliable results and many byproducts, although no racemization was observed.
8. The oxidation to the aldehyde, another possible synthetic intermediate, using a modified Swern oxidation (usual conditions gave complete racemization) (Banfi, L.; Guanti, G.; Narisano, E. *Tetrahedron* , **1993**, *49*, 7385-7392) gave always some extent of racemization.
9. The homologation of the imidazolide, using magnesium salt of monoethylmalonate (Shih, D. H.; Baker, F.; Cama L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29-40) gave complete racemization. Other activated compounds were reacted with lithium enolate of ethyl acetate: S-(2-pyridyl) thioate (Mukayiama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763-4765), mixed anhydride (by reaction with isobutylchloroformate) and N-methoxy-N-methyl amide (for its preparation see: Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818; for the reaction see: Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229-4231). The first two gave only low yields, while the third one did not react at all.
10. **a**) The e.e., accurately measured at the level of cyclized products **3** through bis Mosher ester formation and ^1H-n.m.r., was 78-80%, either starting from **8d** or ***ent*-8d**. We believe that the small percentage of racemization was due to the homologation step. **b**) In order to completely eliminate the slight racemization, we are currently searching for alternative pathways to transform monoprotected alcohols of general formula **5** into **4**.
11. Dangles, O.; Guibé, F.; Balavoine, G., Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984-4993.
12. A very similar method for debenzylation of benzyl ethers is reported: Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661-1664.
13. It is worth noting that reaction of **11** with purified 1,2-*bis*[(trimethylsilyl)thio]ethane under catalysis of various Lewis acids was not successful.

(Received in UK 6 October 1993; accepted 22 October 1993)