Pergamon

Tetrahedron Letters, Vol. 36, No. 22, pp. 3933-3936, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00645-1

Enantioselective Synthesis of the AB ring System of Aklavinone Via a Chemoenzymatic Route

Giuseppe Guanti,* and Renata Riva

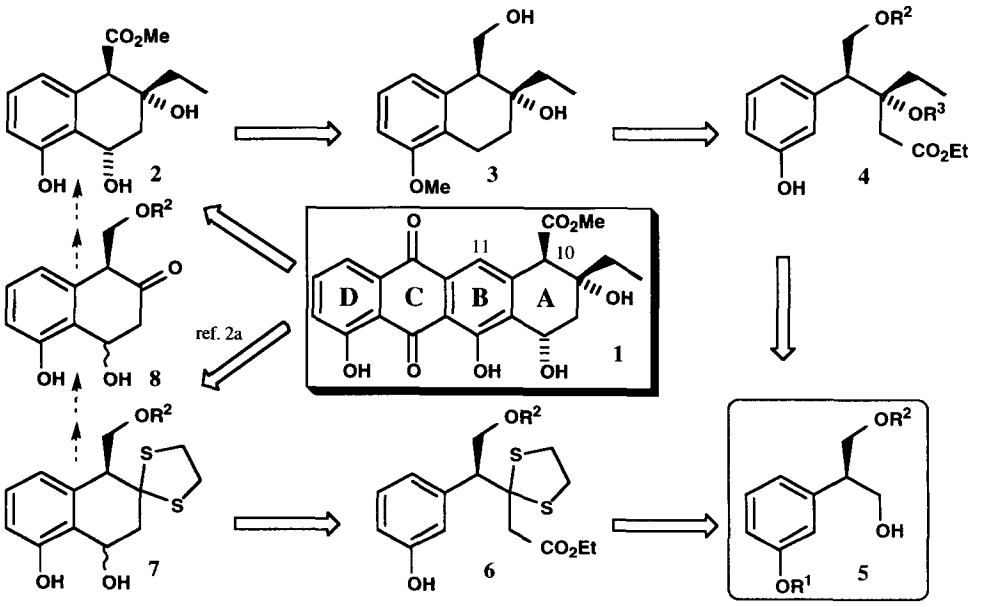
Istituto di Chimica Organica dell'Università degli Studi di Genova, e C.N.R., Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici, corso Europa 26, I-16132 GENOVA (Italy)

Abstract: The AB ring system **2** of aklavinone **1** was obtained using a chemoenzymatic protocol. Key steps are the stereoselective addition of lithium enolate of ethyl acetate to ketone **13** and the intramolecular Friedel-Crafts reaction to give tetralin **17**.

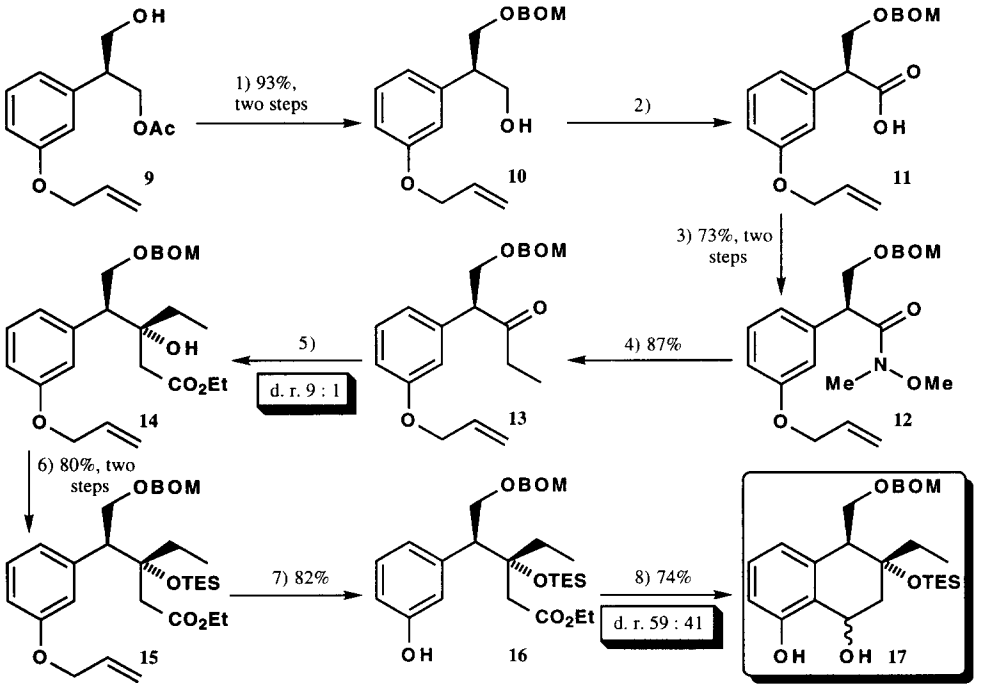
In connection with our studies on the chemistry of 11-deoxyanthracyclinone antibiotics we have recently developed a new strategy for assembling the AB ring moiety of these systems, based on a completely ortho-regioselective intramolecular hydroxyalkylation of 4-(3-hydroxyphenyl)butanoates (Scheme 1).[1]

For this purpose we prepared through a chemoenzymatic procedure[2] the monoprotected diol **5** (R^1 = Allyl; R^2 = Bn), which, after homologation to **6** was successfully cyclized to give **7**.[2a] In our original project

Scheme 1



Scheme 2

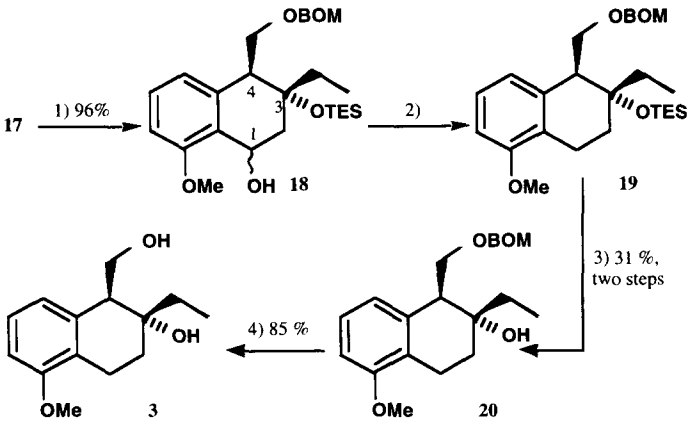


1) a. Benzyloxymethyl chloride, Et*i*-Pr$_2$N, CH_2Cl_2, r. t.; b. KOH, MeOH, r. t.; 2) Jones oxidation, 0°C; 3) MeONHMe· HCl, WSC, THF/H_2O, r. t.; 4) EtMgBr, THF, -78°C; 5) CH_2=C(OLi)OEt, THF, -78°C; 6) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 7) *n*-Bu_3SnH, AcOH, $Pd(PPh_3)_4$, toluene, 80°C; 8) a. DIBALH, CH_2Cl_2, -78°C; b. NH_4Cl, r. t..

this compound, after transformation into **8** by dithiolane removal, had to be transformed into the 1,8-dihydroxytetralin **2** before being coupled with the remaining CD moiety to give the tetracyclic arrangement of **1**. However this route, although original, suffers from some drawbacks deriving from the partial racemization occurring in the homologation step. Moreover, the control of the stereochemistry in the addition of an organometallic to the cyclic ketone **8** is still an open question. Now, while researches directed to the synthesis of **2** through this strategy are still continuing in our laboratory, we explored an alternative way for the transformation of **5** into **2**, which involves first the creation of the chiral center adjacent to the benzylic position on an acyclic ketone before performing the cyclization of **4**, hoping that it could still be done with high regioselectivity. By this way we aimed to overcome the problems occurring in the other route, and we hoped to be able to carry out a more efficient and straightforward synthesis of **2**. The results of these efforts are herein reported.

The chiral monoacetate **9**, obtained with 95% enantiomeric excess ($[\alpha]_D$ = -12.00°)[3] by PPL-catalyzed asymmetrization of the corresponding diacetate (Scheme 2),[2a,4] was protected at the primary hydroxy group as benzyloxymethyl ether. The hydrolysis of the acetoxy group furnished monoprotected diol **10** ($[\alpha]_D$ = + 17.45°), which was readily oxidized to the corresponding carboxylic acid **11**. Activation of crude **11** as the Weinreb's amide[5] **12** ($[\alpha]_D$ = - 40.33°) was accomplished by condensation with N,O-dimethyl hydroxylamine in the presence of the water soluble carbodiimide WSC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] in aqueous medium at pH 4.5.[6] By reaction of **12** with ethylmagnesium bromide we obtained in high yield ketone **13** ($[\alpha]_D$ = - 131.68°), which, by treatment with the lithium enolate of ethyl acetate gave

Scheme 3



1) MeI, K_2CO_3, acetone, reflux; 2) Et_3SiH, $EtAlCl_2$, CH_2Cl_2, -78°C; 3) HF, CH_3CN/ H_2O, 95 : 5, 0°C; 4) H_2, Pd/C, EtOH, r.t..

the corresponding alcohol **14** as a 9 : 1 diastereomeric mixture[7,8] ($[\alpha]_D$ = + 12.27°, for the 9 : 1 diastereomeric mixture).

For further elaboration we protected the tertiary alcoholic group as the triethylsilyl ether[9] to give **15** ($[\alpha]_D$ = - 1.84°, for the 9 : 1 diastereomeric mixture) and deprotected the phenolic function. Finally, ester **16** ($[\alpha]_D$ = - 0.75°, for the 9 : 1 diastereomeric mixture) was treated with 2 equivalents of DIBALH giving, after usual work-up,[1] 1,8-dihydroxytetralin **17** as a 59 : 41 diastereomeric mixture. The good yield of this cyclization reaction was in agreement with the trend previously observed by us,[1] where only arylbutanoates bearing a quaternary carbon at position β gave good results.[10] By transformation of both diastereoisomer of **17** into the bis Mosher ester we demonstrated that in this case no racemization has occurred during the transformation of **9** into **17**!

At this point we had to establish the relative stereochemistry of chiral centres 3 and 4: this was achieved by transforming **17** into diol **3**, a known intermediate in the synthesis of AB ring of aklavinone performed by Meyers.[11] This protocol required the regioselective methylation of phenolic hydroxy group, followed by deoxygenation at the benzylic position 1. The latter reaction turned out to be quite troublesome. Anyway after considerable efforts,[12] we obtained a satisfactory yield of **20**.[13] Deprotection of **20** furnished **3**, whose analytical data (^{1}H-n.m.r, ^{13}C-n.m.r., IR, $[\alpha]_D$) resulted identical with the ones reported by Meyers, confirming that it has the same relative stereochemistry of the natural product.[14] The observed relative stereochemistry of C_3 and C_4 can be explained with a Felkin-Anh model (Figure 1), with the phenyl behaving as the large group.[15]

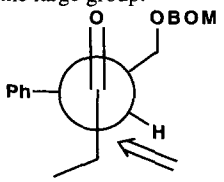


Figure 1

3 Was already converted by Meyers in a four step sequence into the AB ring system of aklavinone. However, in view of the accomplishment of the total synthesis of **1**, probably it is not necessary to deoxygenate the benzylic alcoholic function; although the presence of an epimeric mixture at C_1 may seem an obstacle, it is already known that, after completion of the total synthesis of **1**, it is possible to convert, in a stereocontrolled manner, both epimers into the natural diastereoisomer with α configuration.[16]

In conclusion this new approach utilizes not only original methodologies previously developed in our laboratory, but furnishes also a new entry to the preparation of tetralins having two contiguous stereocenters with the correct relative stereochemistry required by the target.

We wish also to thank M.U.R.S.T. for financial assistance.

REFERENCES AND NOTES

1. Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron* **1994**, *50*, 11945-11966.
2. **a**) For monohydrolysis of 2-(3-alkoxyphenyl)-1,3-diacetoxypropane catalyzed by Pig Pancreatic Lipase (PPL) see: Guanti, G.; Banfi, L.; Brusco, S.; Riva, R. *Tetrahedron Lett.* **1993**, *34*, 8549-8552; **b**) for acetylation in organic solvent of 2-(3-alkoxyphenyl)-1,3-propanediols with PPL supported on celite see: Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron: Asymm.* **1994**, *5*, 9-12 and reference cited in note 3.
3. $[\alpha]_D$ was always measured in $CHCl_3$, using a concentration between 1.2 and 2.0 g/100 mL.
4. We recently demonstrated the absolute configuration of **9** to be *S* (Guanti, G.; Banfi, L., Riva, R. *Tetrahedron: Asymm.*, submitted for publication) by chemical correlation with 3-acetoxy-2-phenylpropan-1-ol obtained through the same enzymatic reaction (see: Guanti, G.; Narisano, E.; Podgorski, T.; Thea, S.; Williams, A. *Tetrahedron* **1990**, *46*, 7081-7092)
5. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
6. The preparation of **12** was not trivial, due to its propensity to give an elimination reaction, most of all at pH > 7: reported conditions represents the best compromise between sufficient concentration of free hydroxylamine and minimization of side reactions.
7. Diastereomeric ratio was determined by ^{1}H-n.m.r.; the two diastereoisomer could not be separated neither at the level of this intermediate nor in one of the following.
8. Addition of lithium enolate of benzyl acetate also works well, giving a 92 : 8 diastereomeric mixture of the corresponding alcohol; however, in this case, the reaction mixture was more difficult to purify.
9. This protection was necessary to perform the cyclization reaction: actually, in the presence of the free alcoholic group the cyclization reaction did not work at all.
10. For a possible explanation of this fact see ref. 1.
11. Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592-4597.
12. Although we had to eliminate an alcoholic function which is usually very reactive, in our case use of neutral conditions [like catalytic hydrogenation (Schmalz, H.-G.; Hollander, J.; Arnold, M; Dürner, G. *Tetrahedron Lett.* **1993**, *34*, 6259-6262; Brockmann, H.; Niemeyer, J.; Brockmann, H. jr.; Bundziekiewicz, H. *Chem. Ber.* **1965**, *98*, 3785-3794) or $NaBH_4$ in the presence of $PdCl_2$ (Satoh, T.; Mitsuo, N.; Nishiki, M.; Nanba, K.; Suzuki, S. *Chem. Lett.* **1981**, 1029-1030)] did not work. On the contrary, some direct deoxygenative methods using acidic conditions [like Et_3SiH in the presence of CF_3CO_2H (Pataki, J.; Harvey, R. G. *J. Org. Chem.* **1987**, *52*, 2226-2230) or BF_3·Et_2O (Adlington, M. G.; Orfanopoulos, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, *34*, 2955-2958)] gave products almost derived from elimination reactions followed by aromatization of ring A. Transformation of hydroxy group into mesylate, tosylate, xanthate or chlorothionocarbonate (Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans 1* **1975**, 1574-1585), iodide (as not isolable intermediate: Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1987**, *28*, 3817-3818), always gave aromatic products. On the contrary, preparation of the imidazolylthiocarbonyl derivative of **18** (Nicolaou, K. C.; Dai, W.-M.; Hong, Y. P.; Tsai, S.-C.; Baldridge, K. K.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 7944-7953), followed by reaction with *n*-Bu_3SnH/AIBN, gave **19** (61%). However, after deprotection of the tertiary alcoholic function, **20** was obtained with about the same yield as reported in Scheme 2, but utilizing a more complicated sequence.
13. Porco, J. A.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410-7411.
14. It must be pointed out that, as expected after definition of the absolute stereochemistry of monoacetate **9**, we obtained the enantiomer of compound described by Meyers and this was confirmed by comparison of $[\alpha]_D$ values [Meyers: + 7.82° (c 0.66, $CHCl_3$); us: -7.71° (c 0.67, $CHCl_3$)].
15. Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456-458.
16. McNamara, J. M.; Kishi, Y. *Tetrahedron* **1984**, *40*, 4685-4691 and references therein.

(*Received in UK* 20 *February* 1995; *revised* 3 *April* 1995; *accepted* 7 *April* 1995)