Pergamon

Tetrahedron Letters, Vol. 36, No. 15, pp. 2607-2610, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00351-7

Total Synthesis of the Macrolide (+)-Aspicilin by an Asymmetrically Catalyzed Macrocyclization of an ω-Alkynal Ester [1)]

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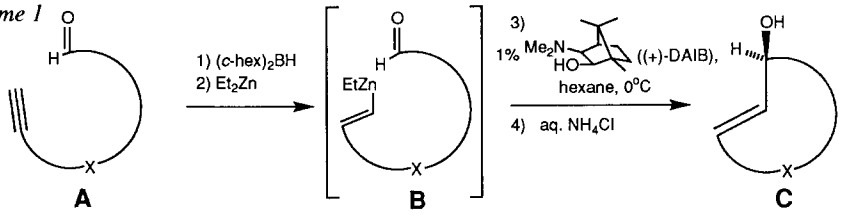
Abstract: ω-Alkynal ester **3**, prepared from (*S*)-propylene oxide **4**, yields the macrocyclic (6*R*)-allylic alcohol **2** (60% yield, 83% d.e.) in one operation *via* monohydroboration, boron/zinc-transmetalation and (-)-DAIB "catalyzed" intramolecular alkenylzinc/aldehyde addition. Introduction of the C(2)-C(3) double bond by selenoxide elimination (**2** → **8**), hydroxy-directed epoxidation (**8** → **9**), acetate assisted α-epoxide opening (**10** →**12**) and acidic methanolysis provides pure (+)-aspicilin (**1**) in 22% overall yield from **4**.

As part of a recent synthesis of the macrocyclic odorant (*R*)-(-)-muscone we presented the asymmetric macrocyclization **A** → **B** → **C** (X = CH_2, Scheme 1). [2)]

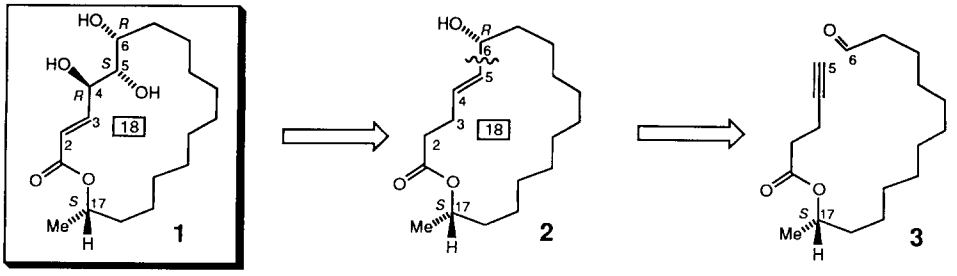
Scheme 1



Thus, one synthetic operation, comprising hydroboration of an ω-alkynal **A**, boron/zinc-transmetalation and dimethylaminoisoborneol "catalyzed" intramolecular addition of the alkenylzinc intermediate **B** to the aldehyde group, furnished a 15-membered carbocyclic (*S*)-allyl alcohol **C** in 75% yield and in high enantiomeric purity.

Analogous ring closure of ω-alkynal esters **A**, containing an ester group X as part of the tether, should offer an interesting approach to macrolides. To prove this idea, we envisaged its application towards a synthesis of (+)-aspicilin, a macrocyclic lactone, isolated from various lichens of the *Lecanoraceae* family (Scheme 2). [3, 5a)]

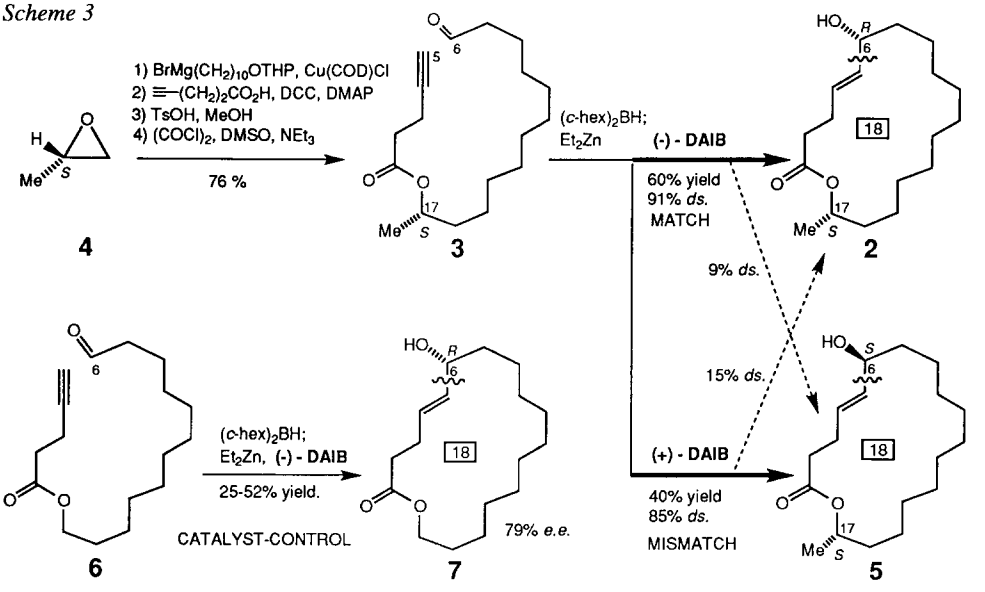
Scheme 2



The structure **1**, follows from degradational/spectroscopic data [4a], an X-ray diffraction analysis [4b, 5a] and from several total syntheses of **1** and its antipode reported by the laboratories of Quinkert [5], Zwanenburg [6], Solladié [7] and most recently, by the Sinha-Keinan team [8]. Our, very different, strategy (Scheme 2) foresees the formation of the C(5)-C(6) bond in the key macrocyclization process **3** → **2**. [9] The (6*R*, *E*)-allyl alcohol **2** should then allow the introduction of the hydroxy groups at C(4) and C(5) with control of the developing stereogenic centers by the existing allylic center C(6).

Starting from pure (*S*)-propylene oxide **4**, epoxide opening with 10-(2-tetrahydropyranyloxy)decylmagnesium bromide/Cu(COD)Cl [5a], esterification of the resulting alcohol with 4-pentynoic acid, acetal cleavage and "Swern-oxidation" furnished the key ω-alkynal ester **3** in 76% overall yield (Scheme 3).

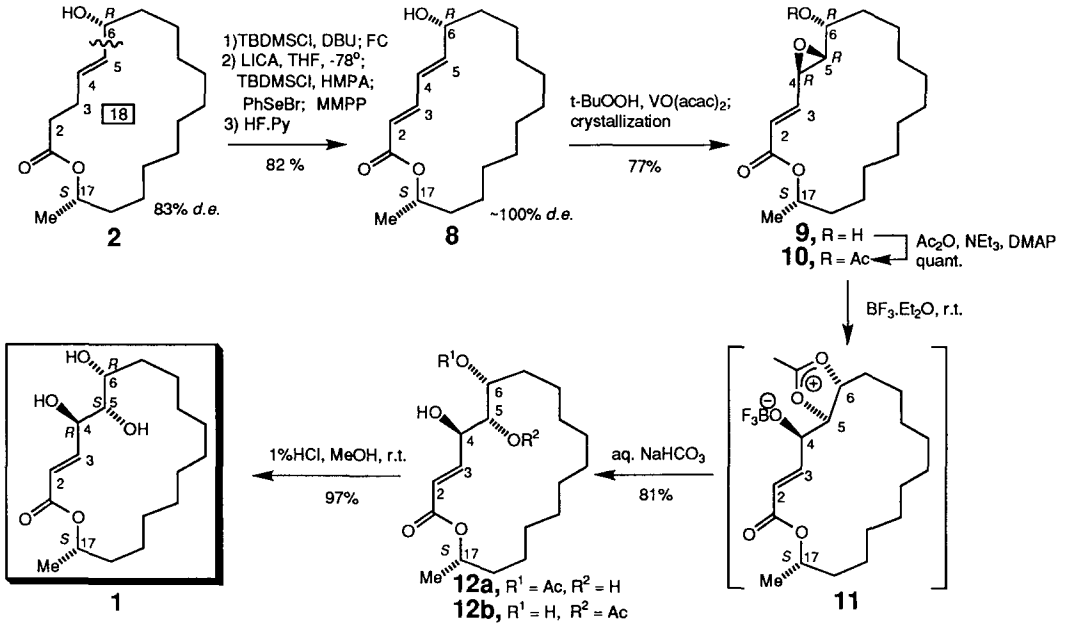
Scheme 3



Now the stage was set for the crucial ring closure. (17*S*)-ω-Alkynal ester **3** was added to a solution of freshly prepared dicyclohexylborane-SMe_2 complex (1 mol equiv.) in degassed hexane under Ar at -20° and the mixture was warmed to 0° over 1 h and then stirred at r.t. for 0.5 h. The resulting solution of alkenylborane was diluted with degassed hexane to 0.05 M and added over 2.5 h at 0° to a 0.05 M solution of diethylzinc (1.5 mol equiv.) in degassed hexane containing (1*R*)-(-)-dimethylaminoisoborneol [(-)-DAIB, 0.01 mol equiv.]. Workup with aq. NH_4Cl provided the expected 18-membered (6*R*)-lactone in 60% chemical yield and in 82% diastereomeric excess.[10] We then tested the influence of the pre-existing center C(17) on the cyclization topicity. Analogous ring closure of the achiral ω-alkynal ester **6** [11], which means solely under the control of (-)-DAIB, proceeded with a slightly diminished stereoselection yielding the (6*R*)-macrolide **7** in 79% enantiomeric excess. [10] More clearly, when we cyclized the (17*S*)-ω-alkynal ester **3** in the presence of (+)-DAIB we obtained the (6*S*)-lactone **5** in only 70% diastereomeric excess [10] which indicates a mismatching of the dominant catalyst bias and the opposing C(17) substituent effect. It thus follows that the (6*R*,17*S*)-lactone **2**, our presumed key intermediate for the (+)-aspicilin synthesis, was formed under the matching of both stereodirecting effects.

To convert the macrocyclic (6*R*)-allylic alcohol **2** into aspicilin (**1**), we chose to introduce the missing C(2)-C(3) double bond prior to the two hydroxy groups (Scheme 4).

Scheme 4



O-Silylation of the alcohol **2** and chromatography, silylation of the lactone group, phenylselenation of the *O*-silylketene acetal, selenide oxidation (magnesium monoperoxyphthalate), selenoxide elimination and fluoride mediated *O*-desilylation furnished the pure (*E,E*)-dienol **8** in 82% overall yield.[12]

Addressing, finally, the bis-hydroxylation of the C(4)-C(5) double bond we envisaged a hydroxy-directed epoxidation, which has already been studied by Quinkert *et al.*.[5c,13] Oxidation of the dienol **8** with vanadyl acetyl acetonate and *t*-butyl hydroperoxide at 0° led to regioselective epoxidation of the allylic double bond, affording a 92:8-stereoisomer mixture which, after flash chromatography and crystallization, provided the major (4*R*,5*R*)-epoxide **9** (m.p. 143.5-145°) in 77% yield.

To open the epoxide regioselectively at the C(5) position with inversion of configuration, alcohol **9** was acetylated and the α-acetoxyepoxide **10** (m.p. 111-112°) treated with boron trifluoride etherate (7 mol equiv.) in dry Et_2O for 3h at r.t.. Subsequent aqueous workup furnished a 1:1-mixture of C(6)- and C(5)-monoacetates **12a/12b** in 81% yield.[14] This result is consistent with a neighboring group assisted α-specific epoxide opening to give a single cyclic oxonium ion **11**, which hydrolysed in both possible directions. Finally, mild acidic methanolysis of the non-separated acetate mixture **12a/12b** (0.08 N HCl/MeOH, r.t., 27 h) gave almost quantitively (+)-aspicilin (**1**), m.p. 151.5-153°; lit. [5c] 152-153°, $[\alpha]_D$ = +39.6 (c = 0.24, $CHCl_3$) ; lit. [5c] $[\alpha]_D$ = +40.7 (c = 0.4, $CHCl_3$) showing the same IR, ^{1}H-NMR, ^{13}C-NMR and MS data as those previously reported.[4a,5a]

In summary, we have obtained optically pure (+)-aspicilin (**1**) from (*S*)-propylene oxide **4** *via* a 12-step sequence in 22% overall yield which compares very favorably with other elegant syntheses of **1** [5-8] and thus exemplifies the potential of intramolecular alkenylzinc/aldehyde additions in the synthesis of chiral macrolides.

Financial support of this work by the *Swiss National Science Foundation* (CHIRAL-2), *Sandoz Pharma Ltd.*, Basel and *Givaudan-Roure AG.*, Dübendorf, is gratefully acknowledged. We thank Mr. *J. P. Saulnier* and Mr. *A. Pinto* for NMR measurements.

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9) The numbering of **1** corresponds to ref. [5] and is also used for all intermediates. All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra.

10) The diastereomeric and enantiomeric excesses (d.e. and e.e., respectively) of the cyclized allyl alcohols were determined by: a) GC of their *O*-acetate (*OV1* column, 25 m, 200°, **2**, **5**), (*Lipodex-E* chiral column, 25 m, 193°, **2**, **5**); b) HPLC of their *O*-3,5-dinitrobenzoyl esters (*Chiracel-OD* chiral column, *i*-PrOH/hexane 2:98, **2**); c) ^{19}F-NMR of their esters derived from (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA): J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543 (**2**); d) ^{19}F-NMR of their (*S*)-MTPA esters (**2**, **7**).

11) Prepared by monoacylation of dodeca-1,12-diol with 4-pentynoyl chloride (1 mol equiv.), NaH (1 mol equiv., THF, 55°, 16 h, 57%) followed by Swern oxidation (91%).

12) Review describing the introduction of (*E*)-α,β-unsaturation in esters and lactones by selenoxide elimination: H. J. Reich, S. Wollowitz, *Org. React.* **1993**, *44*, 1.

13) Dienol **8** has been previously prepared in 3% yield from 1-bromo-9(2'-tetrahydropyranyloxy)nonane by a non-stereoselective 13-step sequence. Dienol **8** gave epoxide **9** and its (4*S*,5*S*)-isomer in ratios of 89:11 (81% yield) and 32:68 (98% yield) upon oxidation with V^{5+}/TBHP and MCPBA, respectively. Acid-catalyzed opening of **9** gave aspicilin **1** in 20% yield: ref. [5c].

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(*Received in Germany* 15 *February* 1995; *accepted* 20 *February* 1995)