Pergamon

Tetrahedron Letters, Vol. 37, No. 49, pp. 8949-8952, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02055-2

Asymmetric Acetate Aldol Reactions in Connection with an Enantioselective Total Synthesis of Macrolactin A

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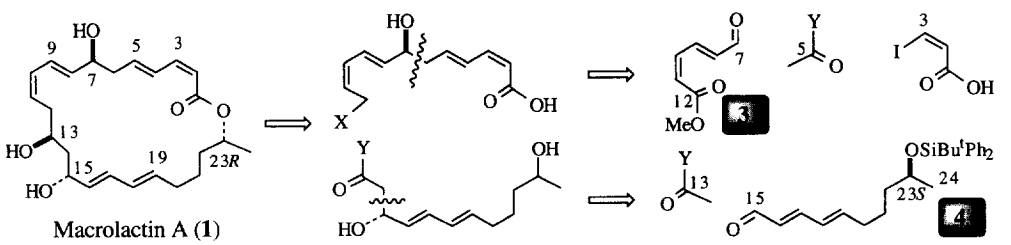
Abstract: Asymmetric aldol-like reactions of cinnamaldehyde, dienal **3** (fragment C7–C12 of macrolactin A), and dienal **4** (fragment C15–C24) with (i) chiral acetylthiazolidinethione-derived enolates, (ii) chiral boron enolates, and (iii) silyl enolates in the presence of chiral titanium–2,2'-dinaphthol complexes are compared. Use of the thiazolidinethione auxiliary and $TiCl_4$ shows practical advantages; e.g., C5–C12 fragment **7** has been isolated enantiomerically pure in 74% yield. Copyright © 1996 Elsevier Science Ltd

Macrolactin A (**1**), the parent aglycone of a novel family of 24-membered polyene macrolides isolated by Fenical et al.[1] from a deep sea bacterium, shows significant inhibition of mammalian *Herpes simplex* viruses and protects T-lymphoblast cells against human HIV viral replication, among other interesting properties.[1] Approaches to some fragments of **1** have been already reported.[2] Very recently, Boyce and Pattenden have achieved the cyclisation, via an intramolecular Stille coupling, of a protected precursor.[3] This has prompted us to advance here our work in connection with a different enantioselective total synthesis of **1** and its congeners.

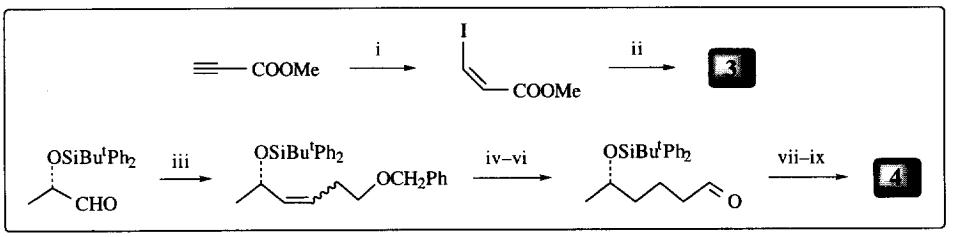
Our strategy is summarised in Scheme 1. The *Z,E* conjugate double bonds were envisaged to be built up by appropriate C_{sp^2}-C_{sp^2} couplings (disconnections C9–C10 and C3–C4, not drawn in Scheme 1) and the *E,E* conjugate system via a Horner–Wadsworth–Emmons reaction (disconnection C18–C19). The stereocenters at C7 and C15 were planned to be formed by means of acetate aldol-like reactions (as shown in Scheme 1). As it is well-known,[4] while the stereochemical outcome of the reaction of aldehydes with chiral enolates arising from ethyl ketones, propionate derivatives, etc. (i.e., from CH_3CH_2COY) can be nowadays controlled with great efficiency, the stereoselectivity of analogous reactions with methyl ketones, acetate derivatives, etc. (i.e., from CH_3COY) is generally much less satisfactory. The target molecule was thus a challenge also in this regard, offering the chance of checking and improving current protocols concerning acetate aldol-like reactions (on conjugate dienals as the substrates, which poses another experimental challenge owing to the fact that the corresponding adducts can be more prone to dehydration than simple β-hydroxy ketones or esters). We report here our studies regarding the reactions of different CH_3COY-derived enolates with (*E*)-PhCH=CH-CHO (cinnamaldehyde, **2**, choosen as a model), with fragment C7–C12 (**3**), and with fragment C15–C24 (**4**).



Scheme 1

Methyl (2*Z*,4*E*)-6-oxohexa-2,4-dienoate (**3**) was prepared from methyl propynoate as shown in Scheme 2: addition of HI to the triple bond to afford methyl (*Z*)-3-iodopropenoate according to the procedure of Lu et al.,[5] followed by a C–C coupling reaction.[6]

The synthesis of dienal **4** started from methyl (*S*)-lactate. Esterification (or lactonisation) of the hydroxy group at C23 under Mitsunobu conditions,[7] toward the end of the total synthesis, was planned in order to reach the wanted configuration (*R*) at this stereocenter.[8] Methyl (*S*)-lactate was readily converted to 2-(*t*-butyldiphenylsilyloxy)propanal in two standard steps (87% overall). Reaction with $Ph_3P{=}CHCH_2CH_2OCH_2Ph$ in THF afforded a *Z*/*E* mixture (11:1) of the expected hex-3-ene derivatives (see Scheme 2);[9] appropriate hydrogenation of the mixture,[10] followed by a Swern oxidation, gave the desired O-protected 5-hydroxyhexan-1-al. This aldehyde was converted to dienal **4** in three steps (Scheme 2, vii–ix): treatment with the *trans* isomer of $(EtO)_2P(O)CH_2$-CH=CH–COOEt (to give a 20:1 *E,E*/*E,Z* mixture, which was easily separated by column chromatography); reduction of the ester to the alcohol with DIBALH; and oxidation to the desired aldehyde.



Scheme 2. (i) LiI·2H_2O, AcOH, CH_3CN, 70 °C, 24 h, 98%; (ii) propenal, $Pd(OAc)_2$ (0.05 equiv), Ag_2CO_3 (1.5 equiv), CH_3CN, 89%; (iii) $Ph_3P^+CH_2CH_2CH_2OCH_2Ph$ Br^-, BuLi, THF, –20 °C, 25 min, 84%; (iv) H_2, Pd/C, AcOEt, Et_3N, rt, 3 h, 100%; (v) H_2, $Pd(OH)_2$, EtOH, 5 h, 100%; (vi) $(COCl)_2$, DMSO, –78 °C, 30 min, Et_3N, rt, 30 min, 98%; (vii) (*E*)-$(EtO)_2P(O)CH_2CH$=CH-COOEt, BuLi, THF–HMPA, –78 °C, 30 min, 74%; (viii) DIBALH (2 equiv), CH_2Cl_2, –78 °C; 20 min, 100%; (ix) MnO_2 (10 equiv), CH_2Cl_2, rt, 16 h, 95%.

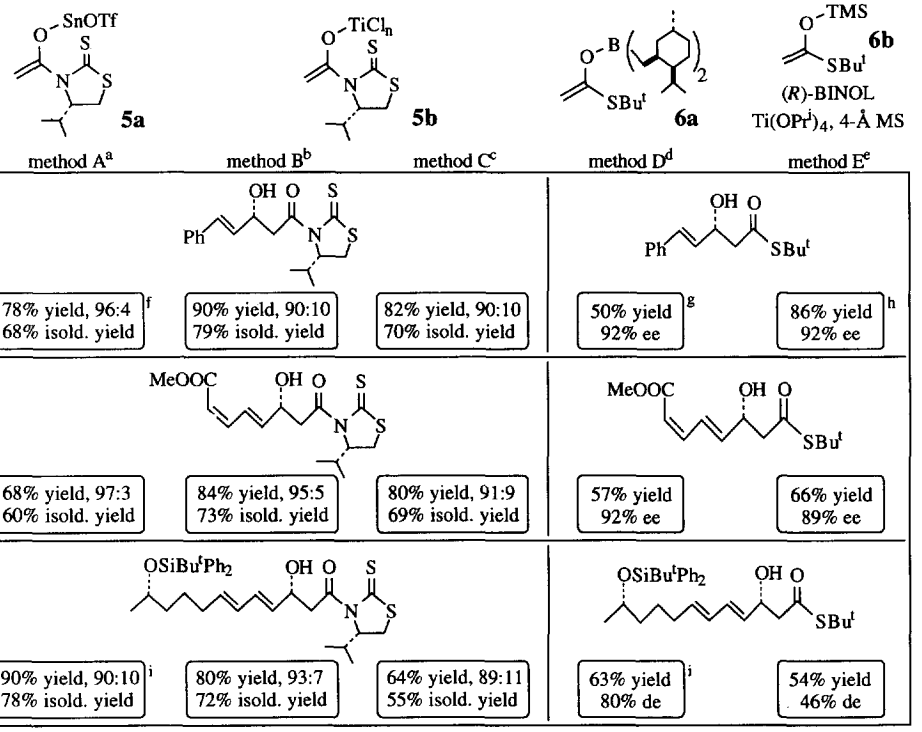
Conjugate aldehydes **2**–**4** were treated with some enolates according to: (i) the procedure described by Nagao et al.[11] (see **5a**); (ii) analogously but using $TiCl_4$ instead of $Sn(OTf)_2$ (see **5b**); (iii) a method based on menthone-derived boron enolates developed by Gennari et al.[12] (**6a**); and (iv) the protocol reported by Keck and Krishnamurthy,[13] on the basis of a Mukaiyama-type aldol reaction catalysed by a BINOL–Ti^{IV} complex (see **6b**). The Ipc enolates of (*S*)-*t*-butyl thioacetate (**6**), by reaction with **2**, afforded only a 36% ee,[14] so that they were not further utilised. Also the Matsukawa–Mikami procedure[15] was investigated (with either phenol, pyrocatechol, 2-chlorophenol, or thiophenol as additives) but, since no practical differences were found with the **6b** case, it will not be further commented.

Table 1 shows the major stereoisomer obtained in each case. It is seen that the reactions of **5a** with **2**–**4** (method A) proceed with excellent diastereoselectivity, and those of **6a** and **6b** (methods D and E, respectively) with **2** and **3** with excellent enantioselectivity. However, from a practical point of view, the procedure based on the work of Nagao et al.[11] but using always an excess[16] of (*S*)-3-acetyl-4-isopropylthiazolidine-2-thione (**5**) and working at –78 °C (except in some experiments with **4**, which appeared to be less reactive than **2** and **3**), the so-called method A in Table 1, was advantageous. In fact, the chemical yields were systematically quite respectable (by contrast to methods D and E) and diastereomers were easily separated by "flash" chromatography. Moreover, recovery of the chiral auxiliary at the end posed no problems.

Since both commercial and aged tin(II) triflate turned out to be unsuitable to generate **5a** from **5**, we used always freshly prepared $Sn(OTf)_2$. As an alternative, we sought for other, less troublesome Lewis acids. It is shown in Table 1 that $TiCl_4$ does the job under similar conditions (method B), affording slightly lower or similar diastereoselections as well as high yields (in such a way that it allowed us, in the case of **3**, to increase up to 73% the isolated yield of the desired stereoisomer); in general, the aldehydes disappeared rapidly and completely, as clearly noted by TLC. Even when only 1.1 equiv of **5b** was employed (method C) the yields

were relatively good. The conclusion is obvious: titanium enolates and Nagao's auxiliary are compatible and do work efficiently for delicate substrates (under mild conditions).

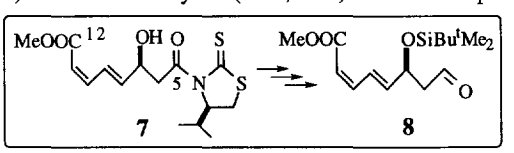
Table 1. Major Stereoisomers from Reactions of Aldehydes **2–4** with Enolates **5a–b** and **6a–b**



[a]Method A: **5**/freshly prepared Sn(OTf)$_2$/*N*-ethylpiperidine (1.7:2.2:2.4) in CH_2Cl_2 at –78 °C for 4–5 h; addition of the aldehyde (1.0) and stirring at –78 °C for ca. 20 min (unless otherwise indicated). [b]Method B: **5** + $TiCl_4$ + $EtPr^i_2N$ (1.7:1.8:1.8) in this order, in CH_2Cl_2 at –40 °C; 2 h later, cooling at –78 °C, addition of the aldehyde (1.0), and stirring for 10 min at –78 °C in all cases. [c]Method C: **5** + $TiCl_4$ + $EtPr^i_2N$ (1.1:1.1:1.1) in this order, in CH_2Cl_2 at –40 °C; 2 h later, cooling at –78 °C, addition of the aldehyde (1.0), and stirring for 10 min at –78 °C. [d]Method D: **6**/(–)-menthone-derived bromoborane/Et_3N (1.1:1.2:1.4) in 1:1 CH_2Cl_2–Et_2O at 0 °C for 1 h; cooling at –78 °C; addition of **2–4** (1.0) and stirring for a few hours. [e]Method E: **6** + LDA in Et_2O at –78 °C for 1 h, then Me_3SiCl at rt for 2 h (95%); catalyst preparation, see ref. 13; aldehydes **2–4** plus 0.20 equiv of Ti^{IV}–BINOL catalyst were cooled at –78 °C; an excess of **6b** (3 equiv) was then added; 18 h at –20 °C without stirring. [f]A 81% yield, referred to **5**, with 94% de, was obtained by Nagao et al. (ref. 11) by using 1.2 equiv of **2**. Golec and Jones reported (ref. 11) a 70% yield of the desired diastereomer. [g]Starting materials were recovered; 65% yield based on consumed **2**. [h]Its enantiomer (89% ee) had been obtained using (*S*)-BINOL (ref. 13). [i]Reaction performed at 0 °C. At –78 °C the stereoselection was slightly better, but the yield was much lower.

Configurations of some major stereoisomers of Table 1 were established by chemical correlation,[17] showing a complete agreement with the expectations from the literature data.[11–13]

From **4** and *ent*-**5b** (prepared from the *R* enantiomer of the thiazolidinethione, $TiCl_4$, and $EtPr^i_2N$) we obtained **7** (the enantiomer of fragment C5–C12 of Table 1) in 74% isolated yield (85%, 95:5). In three simple steps (treatment with Bu^tMe_2SiOTf/2,6-lutidine, reduction with $NaBH_4$ in THF–H_2O, and Swern oxidation) **7** was converted into enantiopure **8**, a suitable intermediate for the total synthesis of **1**, as we expect to report in due course.



Acknowledgments

Thanks are due to the CICYT (Ministerio de Educación y Ciencia) for support (Grant SAF93-0201) and to CIRIT (Generalitat de Catalunya) for a doctorate studentship to A. González (1993–96) and for the Grant GRQ93-1096. Assistance of Katya Vines (1994 European Union post-doc, HCM program, Project ERB CHRXCT93 0141) in the synthesis of compounds related to **3** is also acknowledged. Preparation of menthone-derived haloboranes was carried out by A. G., under the friendly guidance of our network colleagues Prof. Cesare Gennari and Dr. Gilles Pain, in the Università di Milano. Barcelona–Milan traveling expenses of A. G. during 1995 were also granted by the E.U. Project just mentioned.

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8. Methyl (*R*)-lactate was also commercially available when we began this project, but it was/is too much expensive (in relation to the very cheap methyl and ethyl esters of L-lactic acid) to be used as a starting material. Isobutyl (*R*)-lactate is currently a relatively non-expensive substitute for methyl (*R*)-lactate.
9. Analogous reaction with the hydroxy derivative ($Ph_3P^+CH_2CH_2CH_2OH$ Cl^- with 2 equiv of BuLi in THF), according to the procedure reported by Dolle et al. (Dolle, R.E.; Li, C.-S.; Novelli, R.; Kruse, L. I.; Eggleston, D. *J. Org. Chem.* **1992**, *57*, 128) afforded only a 57% yield of hex-3-en-1-ol at best (1:8 *Z*:*E* mixture). Use of $Ph_3P^+CH_2CH_2CH(OR)_2$ Br^- (R-R = $CH_2CH_2CH_2$; cf. Stowell, J. C.; Keith, D. R. *Synthesis* **1979**, 132) and BuLi in THF, at –20 °C gave the corresponding alkene(s) in 82% yield.
10. Performed in two separate steps, as indicated in Scheme 2. One-pot hydrogenation and deprotection, by using H_2 on Pd/C, is not recommended in this case, since the overall yields ranged only between 50% and 67% (the corresponding silanol being obtained as a co-product, probably owing to the allylic nature of the O-silyl substituent). For a related problem, see: Wattanasin, S.; Do, H. D.; Bhongle, N.; Kathawala, F. *J. Org. Chem.* **1993**, *58*, 1611.
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14. Compound **6**/(+)-Ipc_2BCl/Et_3N (1:1:1) in Et_2O at 0 °C for 3 h, cooling at –78 °C, and reaction with **2** (1.0 equiv) for 4 h: 38% yield (56% yield based on consumed **2**), with 36% ee, of the enantiomer depicted in Table 1. These numbers were confirmed with (–)-Ipc_2BCl, from (+)-α-pinene. For the use of Ipc enolates (of methyl ketones), see: Paterson, I. *Pure & Appl. Chem.* **1992**, *64*, 1821, and refs. therein. Ramachandran, P. V.; Xu, W., Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 4911, and refs. therein.
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16. In our case the aldehydes (dienals **3** and **4**) are the most valuable materials.
17. The major stereoisomer arising from the reaction of **2** with **5a** and with **5b**, when treated with an excess of Bu^tSH in CH_2Cl_2, in the presence of K_2CO_3, afforded a product identical (HPLC, Chiralcel column) to the major enantiomer obtained from **2** plus **6a** or **6b**.

(*Received in UK* 7 *October* 1996; *accepted* 18 *October* 1996)