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Use Of N-Boc-*Tert*-Butyldimethylsilyloxypyrrole In Highly Diastereoselective Aldol Reaction

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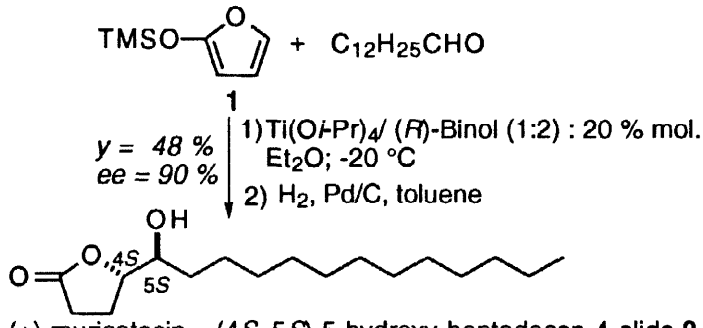
Abstract : (+)-Amino-muricatacin, a non natural aza-analogue of the bioactive annonaceous acetogenin muricatacin was prepared with >99 % d.e. and 68 % e.e., by adddition of N-Boc-*tert*butyldimethylsilyloxypyrrole (TBSOP) on achiral tridecanal in the presence of (*R*)-1,1'-Bi-2-naphtol (Binol), followed by hydrogenation and N-Boc removal protecting group.

Recently we reported the highly enantioselective addition of trimethylsilyloxyfuran **1** (TMSOF) on achiral aldehydes in the presence of (*R*)-1,1'-Bi-2-naphtol (Binol), giving rise to the butenolide adducts in high yields and good diastereo- and enantioselectivity[1]. We have shown the application of this reaction to the expeditive total synthesis of the annonaceous acetogenin, (+)-muricatacin **2**[1,2] (Figure.1).

Figure 1



(+)-muricatacin = (4*S*, 5*S*)-5-hydroxy-heptadecan-4-olide **2**

We were then interested in the extension of this reaction to the pyrrole derivative, namely N-Boc-*tert*butyldimethylsilyloxypyrrole **3** (TBSOP), in order to prepare the corresponding amino-muricatacin **5** which has shown interesting biological properties[3,4]. The use of such reagent **3** for the synthesis of the unnatural amino-muricatacin **5** was described by Casiraghi *et al.*[5], however their strategy required to use an

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enantiomerically pure α-hydroxyaldehyde, which after further chemical transformations led in 8 steps to the desired target molecule. Royer used a trialkylsilyloxypyrrole bearing a chiral substituent on the nitrogen atom for such additions, and observed a good diastereoselectivity[3]. However, extension of this strategy to the use of achiral pyrrole derivative, with the presence of a chiral catalyst is highly desirable, in order to generalize this reaction. In this paper we wish to describe the very efficient use of TBSOP **3** in the presence of (*R*)-Binol for the preparation of (+)-amino-muricatacin **5**. Furthermore, extension of this reaction to other aldehydes would be of great interest for the preparation of more elaborate natural products possessing a 1,2-amino-alcohol group.

N-Boc-*ter*tbutyldimethylsilyloxypyrrole **3** was prepared as already described from N-Boc pyrrolidone[6,7]. Then, N-Boc-*tert*-butyldimethylsilyloxypyrrole was reacted with tridecanal, affording **4**, under different reaction conditions, in order to select the best procedure for a highly diastereo- and enantioselective 1,2-addition (Table and Fig. 2).

Figure 2

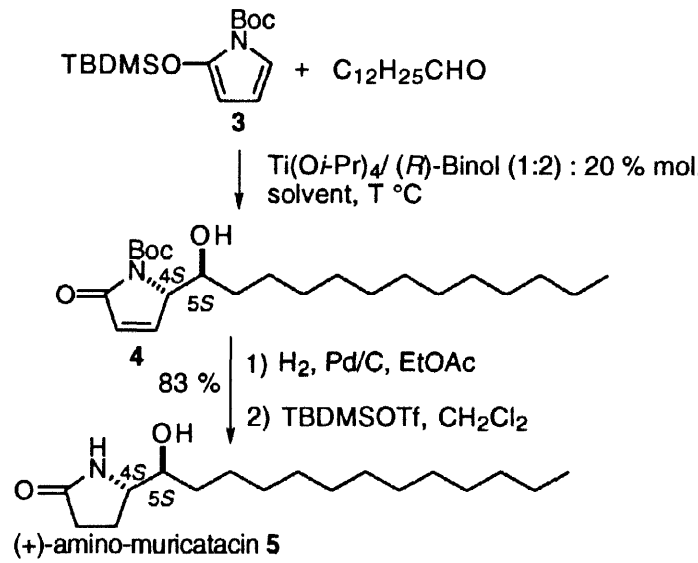

Table : Addition of TBSOP **3** on tridecanal affording **4**

entry	T °C	solvent	isolated yield (%)	*threo:erythro* ratio[a]	ee (%)[b]
1	+20	CH_2Cl_2	46	>99/1	50
2	-20	CH_2Cl_2	NR[c]	-	-
3	-20	CH_2Cl_2	52[d]	>99/1	68
4	-78	CH_2Cl_2	NR[c,d]	-	-
5	-10	Et_2O	28[d]	>99/1	60

a) as judged by GC; b) Enantiomeric excess of the single *threo* diastereomer **4** was determined using the chiral shift reagent [Eu(hfc)$_3$], by ^{1}H NMR analysis; c) NR : no reaction after 1 h; d) with 4 Å MS.

Hydrolysis of the crude reaction products was performed in acidic medium (1M HCl, 10 min. at 20 °C), followed by usual extraction and purification by column chromatography on silica gel. The Binol-Ti(IV)

complex was prepared from the reaction of (*R*)-Binol and Ti(O*i*-Pr)$_4$ in a 2:1 ratio, respectively[8]. Indeed when tridecanal was reacted at +20 °C in CH_2Cl_2 with TBSOP in the presence of 0.2 equiv. of Ti(O*i*-Pr)$_4$ and 0.4 equiv. of (*R*)-Binol, a *single* pair of diastereomer, as determined by ^1H and ^{13}C NMR, as well as by gaz chromatography, was obtained in 46 % yield. The remaining mass balance consisted in the starting aldehyde and the hydrolyzed TBSOP. Enantiomeric excess of the *threo* product **4** was then determined by ^1H NMR analysis in the presence of europium complex (Eu(hfc)$_3$) and showed 50 % ee. Absolute configurations of the major aldol product were then determined as 4*S*, 5*S* by comparison of the sign of optical rotation of the hydrogenated and deprotected product **5**[9] with that reported[3,5]. It is interesting to note that the diastereoselectivity of this reaction is excellent (>99 %) and much better than in the case where $SnCl_4$ was used[5]. It is also better than in the case of addition of trimethylsilyloxyfuran **1** (TMSOF) on tridecanal[1]. On the other hand, enantioselectivity of both reactions are very similar, eventhough in the case of TBSOP **3** the reaction was ran at a slighty higher temperature (+20 *vs* -20 °C). Several factors were then studied in order to improve the ee. We thus decided to perform the reaction at -20 °C, but did not observe the formation of the desired adduct (entry 2). However, after addition of some 4 Å molecular sieves to the reaction medium described above, and when the reaction was performed at -20 °C, we observed in that case a slight increase of the ee (68 *vs* 50 %), with 52 % chemical yield[9] (entry 3). However, when the reaction was ran at -10 °C in diethyl ether in the presence of molecular sieves, the enantioselectivity remained around 60 % in contrast with the TMSOF case[1] (entry 5) albeit in moderate yield. It is worth noting that lowering the temperature (-78 °C) had no effect except to inhibit the reaction. Then, palladium catalyzed hydrogenation of the α,β-usaturated lactam **4** so obtained, followed by removal of the N-Boc protecting group, using *tert*-butyldimethylsilyltriflate as reported[10], afforded (+)-amino-muricatacin **5** in 83 % yield for the last two steps (and 68 % e.e.). It is worth noting that this 3-steps synthesis of (+)-aminomuricatacin **5** is the most expeditive and efficient preparation of this biologically active product, reported so far.

In conclusion, these results described for the first time the enantioselective addition of TBSOP **3** on achiral aldehydes, to form the expected unsaturated lactams in a highly diastereo- and enantiomeric pure form. This reaction finds an application to the synthesis of unnatural amino-muricatacin, but allows one to prepare in a single step chiral building blocks which possess *two contiguous stereogenic centers bearing two heteroatoms,* whose absolute configurations are under the catalyst control. The structure of the catalyst remains unknown, however a tentative schematic view has been given, by Bach[11] and in related studies reported by Corey[12], in which (*R*)-Binol displaced two (O*i*-Pr) ligands. Further developments of this reaction in order to improve the chemical yield and the e.e., as well as uses of different aldehydes and new electrophiles are now under investigations in our laboratory.

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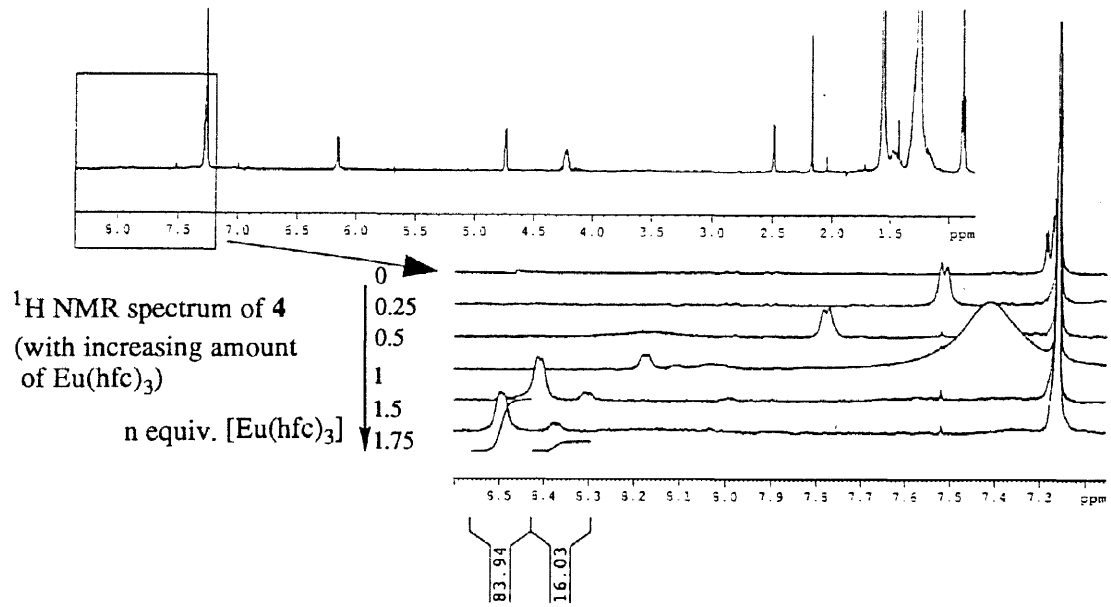
(9) Spectroscopic data of **4** : $[\alpha]_D^{20}$ = +123 (c 0.33, $CHCl_3$); ^1H NMR (250 MHz, ref. $CHCl_3$, δ-ppm) : 7.28 (1H, dd, J = 6.17, 2.12 Hz), 6.15 (1H, dd, J = 6.16, 1.76 Hz), 4.73 (1H, td, J = 5.19, 1.34 Hz), 4.21 (1H, m), 2.50 (1H, br.s, OH), 1.55 (9H, s), 1.42 (2H, m), 1.23 (20H, br. s), 0.88 (3H, t, J = 7 Hz) ; ^{13}C NMR (50 MHz, ref. $CDCl_3$, δ-ppm) : 169.37, 150.18, 148.66, 127.38, 83.45, 71.12, 66.77, 31.85, 31.02, 29.56, 29.33, 28.04, 25.74, 22.63, 14.06.
Spectroscopic data of **5** (^1H and ^{13}C NMR, MS, IR) are identical to the literature data[3]; $[\alpha]_D^{20}$ = +4.5 (c 0.6, $CHCl_3$) ($[\alpha]_D^{20}$ lit[3]. = +5 (c 2.1, $CHCl_3$)).



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