Highly Enantioselective 1,2-Addition of 2-[(Trimethylsilyl)oxy]furan to Aldehydes: Application to Muricatacin Synthesis

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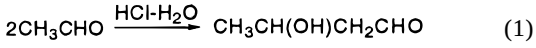
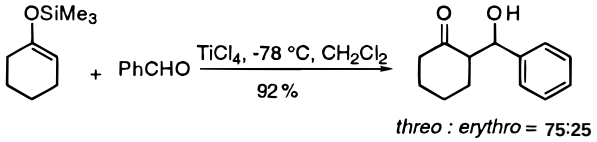
TMSOF 2-[(trimethylsilyl)oxy]furan has been used in an enantioselective aldol reaction for the first time. Indeed, addition of TMSOF to achiral aldehydes, in the presence (*R*)-1,1′-bi-2-naphthol (Binol), gave the corresponding butenolides with moderate diastereomeric ratios (dr = 60%) and ee's between 60 and 90%. Application of this reaction to the total synthesis of annonaceous muricatacin in only two steps (in regards to the numerous multistep syntheses published so far) illustrated the efficiency of this strategy.

Aldolization is probably one of the most important reactions in organic synthesis for carbon−carbon bond formation. Wurtz was one of the earliest authors to use the name *aldol* for the product, obtained after exposing an aldehyde to acid conditions, because of the presence of a hydroxyl as well as a carbonyl[1] (eq 1).



(1)

However, synthetic uses of this reaction were extremly limited due to the low yield of homocoupled products, until Mukaiyama showed that trialkylsilyl enol ethers add to aldehydes and ketones to form cross-heterocoupled aldols with good diastereoselectivity and good chemical yields[2] (eq 2). Influence on the stereochemical outcome of both the reaction conditions as well as the configuration of the double bond on the aldolization has been studied.

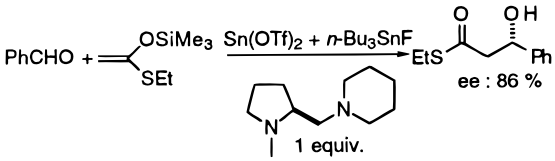


(2)

threo : erythro = 75:25

Much effort to achieve this reaction under asymmetric catalysis was made by several groups which finally succeeded in a highly enantioselective addition of trimethylsilyl enol ethers of thioesters to aldehydes and ketones, in the presence of a chiral diamine[3] (eq 3). Since then the reaction found many applications with various enols derived from carboxylic acids derivatives (e.g. esters, thioesters, amides, etc.) as well as from ketones, in the presence of chiral catalysts.

2-[(Trimethylsilyl)oxy]furan (TMSOF) is a very convenient, commercially available nucleophile which reacts with many electrophiles to lead to the formation of



(3)

butenolides, which are very often encountered in naturally occurring products and which may also serve as useful chiral building blocks for the formation of polysubstituted γ-lactones as well as for the preparation of products possessing a 1,2-diol function. For instance, Casiraghi has used TMSOF with homochiral α-hydroxy aldehydes as electrophiles.[4] We have shown that TMSOF can also be used in highly diastereoselective C-glycosylations for the preparation of oligo tetrahydrofurans.[5] Recently Katsuki has shown that TMSOF reacts with Michael acceptors to form the 1,4-addition products in an enantioselective manner.[6] Takei and then Jefford reported, respectively, in 1977 and in 1987 that TMSOF adds to achiral aliphatic aldehydes with good to excellent diastereomeric ratios depending on the nature of the Lewis acid used.[7] However, to the best of our knowledge no reports on the asymmetric version of this reaction

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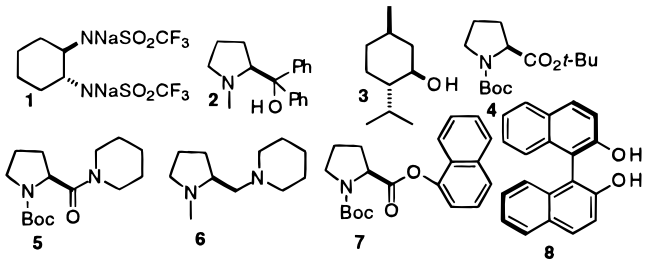
Table 1. Addition of TMSOF to Octanal

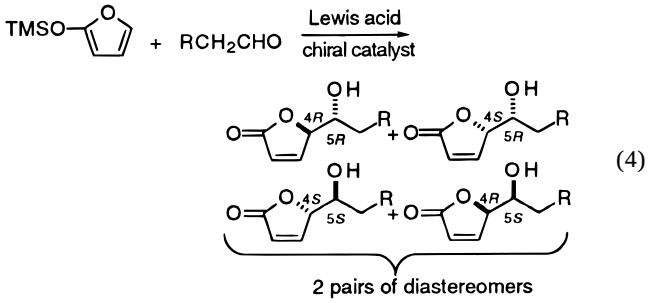
entry	Lewis acid[a]	isolated yield (%)	syn/anti ratio
1	$BF_3{\cdot}OEt_2$	95[b]	81:19
2	$TiCl_4$	78	79:21
3	$SnCl_4$	62	70:30
4	$SnCl_2$	58	90:10
5	$Sc(ClO_4)_3$	80	85:15
6	$TrClO_4$	63[c]	80:20
7	$Ti(O\textit{i}\text{-}Pr)_4$	0[d]	–
8	$Ti(O\textit{i}\text{-}Pr)_4$	0[c,d]	–
9	$\textit{n}\text{-}Bu_4NF$	25	28:72

[a] All reactions were run at −78 °C in CH_2Cl_2 with 1 equiv of the catalyst. [b] Reference 7, reaction performed with hexanal. [c] At −20 °C. [d] Octanal was recovered unchanged.

Chart 1



have appeared in the literature (eq 4). Indeed, this reaction would provide interesting homochiral compounds possessing two contiguous stereogenic centers which could be used as building blocks for more elaborate compounds.



(4)

Therefore, 2-[(trimethylsilyl)oxy]furan was separately reacted with octanal in the presence of different Lewis acids, under different reaction conditions, to select the best procedure for a highly diastereoselective 1,2-addition (Table 1).

The reactions generally gave a mixture of the free aldols and the corresponding TMS ethers. Therefore, acidic hydrolysis of the crude reaction products was performed (1 M HCl, 1 h at 20 °C), prior to purification by column chromatography on silica gel. In view of these results, $SnCl_2$ catalysis gave the best syn/anti ratio (90:10), albeit in moderate 58% yield, while titanium ($TiCl_4$) and scandium ($Sc(ClO_4)_3$) catalysts provided the best yields in 79:21 and 85:15 syn/anti ratios, respectively. Surprisingly, in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ catalyst, we did not observe any coupled product, and the aldehyde was recovered unchanged even when the reaction was run at −20 °C (entries 7 and 8). We then studied the influence of several asymmetric catalysts on the course of the reaction (Chart 1). The results are summarized in Table 2.

Chiral catalysts **1**−**7** gave poor results in terms of enantioselectivity, since almost no enantiomeric excess could be measured on the crude mixtures (entries 1−17),

Table 2. TMSOF Addition to Octanal at −78 °C in CH_2Cl_2 in the Presence of Both Various Asymmetric Catalysts and Lewis Acids

entry	catalyst	Lewis acid	isolated yield (%)	syn/anti ratio	ee (%)[a]
1	**1**	$TiCl_4$ (stoic)	57	70:30	0
2	**1**	$TiCl_4$ (cat)	39	80:20	0
3	**1**	$Sc(ClO_4)_3$ (cat)	77	80:20	0
4	**1**	$SnCl_4$ (cat)	70	70:30	0
5	**4**	$SnCl_4$ (cat)	38	65:45	0
6	**5**	$SnCl_4$ (cat)	40	60:40	0
7	**7**	$SnCl_4$ (cat)	33	70:30	0
8	**6**	$SnCl_4$ (cat)	15	80:20	0
9	**6**	$SnCl_4$ (stoic)	NR[b]	-	-
10	**6**	$TiCl_4$ (stoic)	53	70:30	0
11	**2**	$SnCl_4$ (cat)	90	80:20	+/− 2
12	**2**	$\textit{n}\text{-}Bu_3SnF$, $Sn(OTf)_2$ (cat)	80	55:45	0
13	**6**	$\textit{n}\text{-}Bu_3SnF$, $Sn(OTf)_2$ (cat)	CM[c]	-	-
14	**2**	$SnCl_4$ (stoic)	80	60:40	0
15	**1**	$Yb(OTf)_3$ (cat)	NR[b]	-	-
16	**3**	Sm (cat)	30	25:75	0
17	**3**	Sm (cat)	43[d]	25:75	0
18	**8**	$Ti(O\textit{i}\text{-}Pr)_4$	95[e]	70:30	57
19	**8**	$Ti(O\textit{i}\text{-}Pr)_4$	56[e,f]	80:20	76
20	**8**	$Ti(O\textit{i}\text{-}Pr)_4$	50[e,g]	53:47	87
21	**8**	$Ti(O\textit{i}\text{-}Pr)_4$	25[h]	77:13	10

[a] Enantiomeric excess of the major isomer were determined using the chiral shift reagent [Eu(hfc)$_3$], by ^{1}H NMR analysis. [b] NR: no reaction. [c] CM: complex mixture. [d] In THF. [e] At −20 °C. [f] With 4 Å MS. [g] In ether. [h] 2 h.

except with prolinol **2** which allowed us to observe a minute asymmetric induction (entry 11). Then, even though $Ti(O\textit{i}\text{-}Pr)_4$ did not give the expected coupled products in the absence of asymmetric catalyst, we decided to use it in the presence of (*R*)-1,1′-bi-2-naphthol (Binol) **8**, since it has been proven that the complex so formed is a ligand accelerating. The Binol−Ti(IV) complex is prepared from the reaction of (*R*)-Binol and $Ti(O\textit{i}\text{-}Pr)_4$ in a 2:1 ratio, respectively.[9] Indeed when octanal was reacted at −20 °C in CH_2Cl_2 with TMSOF in the presence of 0.2 equiv of $Ti(O\textit{i}\text{-}Pr)_4$ and 0.4 equiv of (*R*)-Binol, a hardly separable 70:30 mixture of syn/anti aldols was obtained in 95% combined yield. Enantiomeric excess of the major product was then determined by NMR analysis in the presence of europium complex ($Eu(hfc)_3$) and showed that the syn (or threo) product was obtained with 57% ee. Absolute configurations of the major aldol product were then postulated as 4*S*,5*S* by comparison of the sign of optical rotation of the hydrogenated product with that reported for related compounds,[10,11] and confirmed in the case of preparation of (+)-muricatacin (see below). We then decided to perform the reaction in the presence of 4 Å molecular sieves and a 1:1 mixture of (*R*)-Binol−$Ti(O\textit{i}\text{-}Pr)_4$ and observed a slight increase of the ee of the major threo isomer (76 vs 57%), but in a lower isolated yield (entry 19). However, when the reaction was run in diethyl ether, the enantioselectivity dramatically increased (87% ee, entry 20) albeit in moderate yield. It is worth noting that lowering the temperature (−78 °C) did not provide an increase in the stereoselec-

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Table 3. TMSOF Addition to Various Achiral Aldehydes, in the Presence of Ti(IV):(*R*)-Binol at −20 °C in CH_2Cl_2

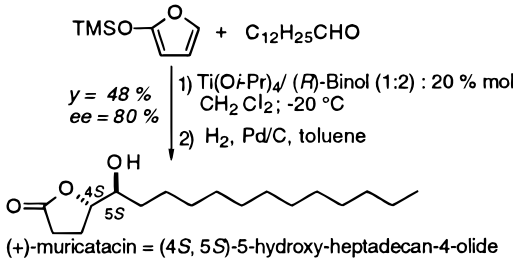
entry	R[a]	yield (%)	syn/anti ratio	ee[b] (%) [abs config][c]
1	*n*-C_7H_{15}	95	70:30	57 [*S*,*S*]
2	*n*-C_7H_{15}	50[d]	53:47	87 [*S*,*S*]
3	*n*-$C_{12}H_{25}$	80	60:40	80 [*S*,*S*]
4	*n*-$C_{12}H_{25}$	20[d]	70:30	90 [*S*,*S*]
5	Ph	70	70:30	54 [ND]

[a] R of RCHO. [b] Enantiomeric excess of the major isomer was determined using the chiral shift reagent [Eu(hfc)$_3$], by ^{1}H NMR analysis. [c] Of threo product. [d] In Et_2O.

tivity of the reaction (entry 21), but gave poor ee (10%). This suggested that the reaction is auto-induced. However, more experiments are needed to confirm this explanation. Next we decided to study the reaction with various aldehydes, and the results are tabulated in Table 3.

Addition of TMSOF in CH_2Cl_2 to aliphatic aldehydes gave excellent results in terms of chemical yield and enantioselectivity. However, the aromatic aldehyde gave a lower ee. In contrast when the reactions were run in Et_2O, the enantioselectivity was in all cases better, albeit the addition occurred in moderate yields and some of the starting material (aldehyde) was recovered. Absolute configurations of the adducts on aliphatic aldehydes were determined, after hydrogenation of the double bonds, by comparisons of the sign of specific rotations of the reduced products with related compounds.[10,11] In the case of benzaldehyde, we assume that the major aldol product has the 4*R*,5*R* configurations since the sign of the specific rotation is opposite to those of the aliphatic aldol products. This inverse inductive effect has already been observed in a related case by Shibasaki.[3d] We then applied this new methodology to the efficient and rapid synthesis of natural muricatacin, a natural metabolite of the bioactive annonaceous acetogenins.[12] Since the discovery of this cytotoxic hydroxy-butyrolactone, about 17 different total syntheses were reported in the literature.[4b,13] Therefore, TMSOF was added to tridecanal in the presence of (*R*)-1,1′-bi-2-naphthol (Binol) **8**, at −20 °C in CH_2Cl_2 as described above. ^{1}H NMR analysis, in the presence of Eu(hfc)$_3$, of the mixture of butenolides showed that the major threo product was obtained with 80% ee. This is probably due to the steric hindrance of the long aliphatic chain (compare entries 1 and 3, Table 3) which cannot be seen as an extanded chain but rather as a "bowl". When the reaction was run in Et_2O, it is noteworthy that the major threo product was obtained, in this case with 90% ee. The resulting mixture of the aldols was then hydrogenated over palladium, and flash chromatography on silica gel allowed us to isolate the pure (4*S*,5*S*)-5-hydroxy-hepadecan-4-olide, namely (+)-muricatacin. Recrystallization of muricatacin[14] should allow us to increase the ee (Scheme 1).

Scheme 1



In conclusion, these results describe the first enantioselective addition of TMSOF on achiral aldehydes, to form the expected butenolides in a highly enantiomeric pure form. This reaction finds an application to the synthesis of natural muricatacin, but allows single-step preparation of chiral building blocks which possess two contiguous stereogenic centers substituted by two hydroxyls whose absolute configurations are under catalyst control. The structure of the catalyst remains unknown; however, a tentative schematic view has been given by Bach[15] in which (*R*)-Binol displaced (O*i*-Pr) ligands. Further development of this reaction in which aldehydes are replaced by different electrophiles is now under investigation in our laboratory.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, using $CDCl_3$ as solvent and internal reference. EI-MS were obtained at an ionization potentiel of 40 eV, CI-MS with NH_3, and otherwise as indicated. Toluene and THF were distilled over sodium−benzophenone, and CH_2Cl_2 over CaH_2 immediately prior to use. Molecular sieves (4 Å) were dried at 100 °C for a *minimum* of 12 h prior to use. Aldehydes were obtained commercially and used without purification. Chiral ligands **1**, **2**, **3**, and **8** were purchased from Aldrich, and compounds **4**−**7** were synthesized as previously reported.[16] SiO_2 (from Riedel-de Haën, 230−400 mesh) was used for the purifications by flash chromatography.

CH_2Cl_2 Representative Procedure. As a typical procedure, preparation of (+)-2,3-deshydromuricatacin from tridecanal is given as follows: (*R*)-1,1′-bi-2-naphthol (114 mg, 0.4 mmol) and Ti(O*i*-Pr)$_4$ (59 μL, 0.2 mmol) are stirred in 4 mL of CH_2Cl_2 at room temperature for 1 h. To this red-brown colored solution is added tridecanal (198 mg, 1 mmol) in 3 mL of CH_2Cl_2, the temperature is brought to −20 °C, and then 2-[(trimethylsilyl)oxy]furan (0.25 mL, 1.5 mmol) is added. After stirring 1.5 h at this temperature, 5 mL of NH_4Cl are added followed by 5 mL of 1 M HCl, and the reaction mixture is stirred at 20 °C for 1 h. After extraction of the organic layer with 3 × 5 mL of EtOAc, the combined organic phases are dried over $MgSO_4$, filtered, and concentrated under vacuum. Then purification by flash chromatography on silica gel (cyclohexane/EtOAc: 60/40) led to 212 mg (80%) of the threo/erythro (60/40) mixture of the expected butenolides, (4*S*,5*S*)- and (4*S*,5*R*)-5-(1′ hydroxytridecanyl)furan-2(5*H*)-one or 2,3-deshydromuricatacin (for ee of major diastereomer, see Table 3).

CH_2Cl_2 with Molecular Sieves 4 Å. Representative Procedure. (*R*)-1,1′-Bi-2-naphthol (28.5 mg, 0.1 mmol) and

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(14) However, the reaction was run on 1 mmol scale and did not allow us to recrystallize (+)-muricatacin.

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$Ti(O\textit{i}\text{-}Pr)_4$ (29.5 μL, 0.1 mmol) with 400 mg of molecular sieves 4 Å are stirred in 2 mL of CH_2Cl_2 under reflux for 2 h. Then, after cooling to room temperature, octanal (77.5 μL, 0.5 mmol) is added, the temperature is lowered to −20 °C, and then 2-[(trimethylsilyl)oxy]furan (0.125 mL, 0.75 mmol) is added. After stirring 1.5 h at this temperature, the reaction is hydrolyzed as above, and identical workup led to 59 mg (56%) of the threo/erythro (80/20) mixture of the expected butenolides, or (1′*S*,5*S*)- and (1′*R*,5*S*)-5-(1′-hydroxyoctanyl)furan-2(5*H*)-one (for ee of major diastereomer, see Table 2).

Et_2O Representative Procedure. (*R*)-1,1′-Bi-2-naphthol (57 mg, 0.1 mmol) and $Ti(O\textit{i}\text{-}Pr)_4$ (29.5 μL, 0.1 mmol) are stirred in 2 mL of Et_2O at room temperature for 1 h. To this red-brown colored solution is added octanal (77.5 μL, 0.5 mmol), the temperature is brought to −20 °C, and then 2-[(trimethylsilyl)oxy]furan (0.125 mL, 0.75 mmol) is added. After stirring 1.5 h at this temperature, the reaction is hydrolyzed as above, and identical workup led to 53 mg (50%) of the threo/erythro (53/47) mixture of the expected butenolides, or (1′*S*,5*S*)- and (1′*R*,5*S*)-5-(1′-hydroxyoctanyl)furan-2(5*H*)-one (for ee of major diastereomer, see Table 2).

Preparation of (+)-Muricatacin. Then, the mixture of 2,3-deshydromuricatacin obtained in CH_2Cl_2 (212 mg, 0.8 mmol) is hydrogenated over Pd/C (200 mg) in toluene at room temperature for 12 h. Filtration of the crude reaction mixture through a pad of silica gel, followed by concentration under vacuum and purification by flash chromatography, led to 125 mg of (+)-muricatacin and to 80 mg of (+)-5-*epi*-muricatacin. Spectral data (NMR, mass spectrometry) and specific rotation of both compounds are in agreement with reported values (see refs 11 and 13d).

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Supporting Information Available: Physical and spectral listings and a selected ^1H spectrum of the new compounds (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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