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HIGHLY STEREOSELECTIVE ACETYLATIONS VIA NOREPHEDRINE DERIVED OXAZOLIDINES.

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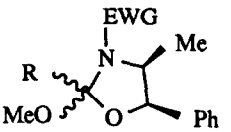
Abstract: *Norephedrine derived 2-methoxy-2-methyl oxazolidine 2 is an efficient stereoselective acetylating agent in reactions with stereogenic silylenolethers and silylketenethiolacetals Moderate selectivity is also obtained upon acetylation of crotyltin reagents The present methodology compares favorably with the previously reported enantioselective Claisen-type acylations*

Introduction

We recently introduced norephedrine derived 2-methoxy oxazolidines **1** (Fig 1) as chiral equivalents of the formyl cation [1]

Figure 1

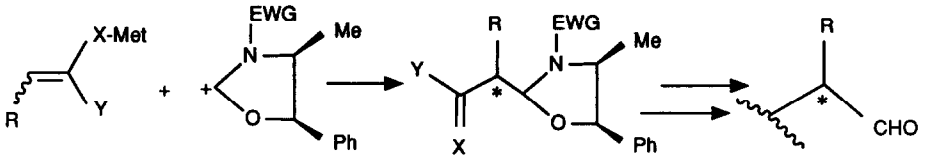


1 R= H **a** EWG= Cbz
b EWG= Ts

2 R = Me , EWG = Cbz

Treatment of **1** with Lewis acids gives rise to the corresponding cations, whose formation, properties, and thermal stability have been studied by NMR spectroscopy [2] Addition of stereogenic nucleophiles, such as silylenolethers and silylketeneacetals or crotyltin reagents, followed by cleavage of the oxazolidine ring and carbonyl demasking constitutes an easy process of enantioselective formylation (Scheme 1)

Scheme 1



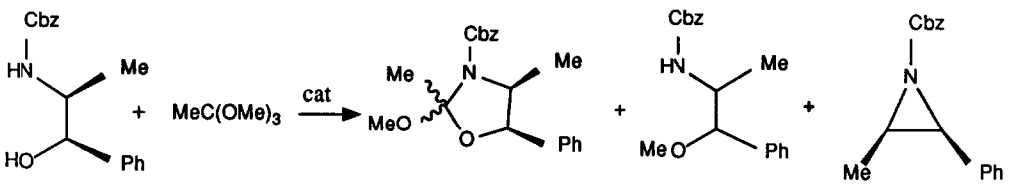
X= $OSiR_3$, NR_2, SnR_3 Y= SR, OR, R, H X= O, CH_2

The application of the same synthetic scheme to 2-alkyl substituted oxazolidines would provide an interesting extension of our methodology to the more general case of enantioselective acylation The goal appeared particulary attractive, since only a few chiral equivalents of the acyl cation capable of discriminating between the enantiotopic faces of stereogenic nucleophiles have appeared in the literature [3] We therefore set about investigating this possibility using 2-methyloxazolidine **2** as a model case

Results and discussion

The synthesis of **2** proved to be much more problematic than that of the parent compound **1** Application of the usual conditions[1d] (pyridinium tosylate catalyst in refluxing benzene) to the condensation of N-Cbz-norephedrine with trimethylorthoacetate gave rise to at least three different products This mixture contains the expected condensation adduct **2** together with products of norephedrine degradation, which were tentatively identified as **3** and **4** (Scheme 2)

Scheme 2

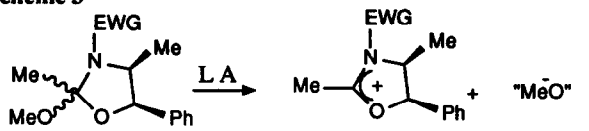


2 **3** **4**

Optimum conditions for the synthesis of **2** were finally achieved by adding the catalyst (pyridinium tosylate, 15 %) to a refluxing solution of N- Cbz-norephedrine and trimethylorthoacetate in benzene In this way the concentration of the reactive dioxolenium cation is maximized and condensation is attained before the competing process of ephedrine degradation takes place

With a convenient synthesis of **2** in hand, we proceeded to investigate its reactivity toward acid catalyzed nucleophilic addition Our NMR studies[2] indicate that cation **5** could be formed by addition of either 1 eq of $TiCl_4$ or 2 5 eq of BF_3-Et_2O at -78°C in CD_2Cl_2 (Scheme 3) In the presence of $TiCl_4$, **5** is stable only for a few hours at -20°C On the contrary when the cation is generated with BF_3-Et_2O its NMR spectrum remains unchanged for days at room temperature

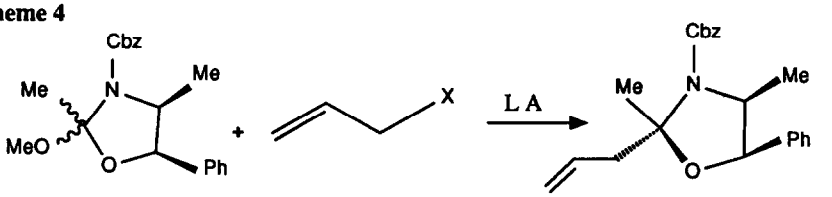
Scheme 3



2 5

This feature could be exploited in addition to weak allylmetal reagents For instance, allylsilane addition (Scheme 4) cannot be achieved below room temperature, and therefore $TiCl_4$ cannot be used as a promoter for this reaction (Table 1, entry 2)

Scheme 4



6 X = Me_3Si

2

7 X = Bu_3Sn

Table 1 Acid catalyzed addition of allylmetal reagents **6** and **7** to **2**[a]

Entry	Reagent (eq)	Lewis acid (eq)	Conditions	Yield[b]
1	**6**	BF_3-Et_2O(2)	-20 → RT,18h	26%
2		$TiCl_4$(1)	-78 → -20°C	=
3	**7**	BF_3-Et_2O(2)	0°C → RT, 2h	77%
4		$TiCl_4$(1)	-20°C, 4h	40%

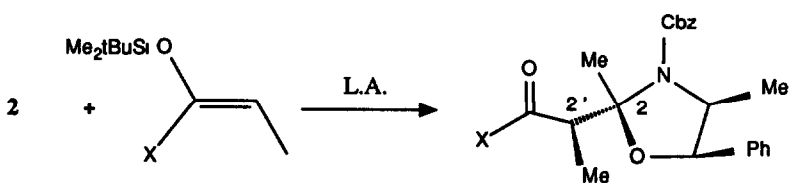
a All reactions were carried out by adding the Lewis acid to a solution of **2** and the indicated reagent in dichloromethane and in the presence of 4A molecular sieves b Isolated product

The addition can be accomplished using BF_3-Et_2O (Table 1, entry 1), but in low yields Better results can be achieved with the more reactive tributyltin compound **7** (Table 1, entries 3 and 4) In every case the reaction product appears to be a single isomer by GLC and high temperature ^{1}H-NMR spectroscopy [4] In keeping with the previously studied addition reactions of **1**, stereochemistry at C-2 was assumed to be R This corresponds to addition of the nucleophile to the least hindered side of the cationic ring More rigorous stereochemical proof will be provided for the cases of reaction with stereogenic nucleophiles (vide infra)

Addition of stereogenic silylenolethers and silylketenethiolacetals to **2** turned out to be highly stereoselective (Scheme 5, table 2) Reaction between silylketenethiolacetal **8** and **2** in the presence of $TiCl_4$ resulted in the isolation of a single isomer **10** (Table 2, entry 1) in 57 % yield Use of BF_3-Et_2O or $SnCl_4$ as promoters (Table 2, entries 2 and 3) does not modify the stereochemical outcome, but **10** is obtained in

lower yields $TiCl_4$ appeared to be the promoter of choice also for the addition of diethylketone silylenolether **9** Compound **11** was again isolated as a single isomer by NMR spectroscopy

Scheme 5



8 X = StBu **10** X = StBu

9 X = Et **11** X = Et

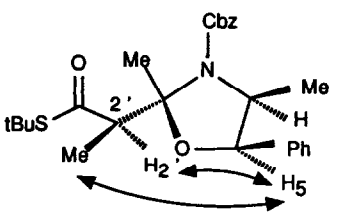
Table 2 Acid catalyzed addition of **8** and **9** to **2**

Entry	Reag	L A	Conditions	Yield	Prod	d r
1	**8**	$TiCl_4$	15h,-20°C	57 %	**10**	≥ 22 1
2		BF_3-Et_2O	24h, RT	23 %	**10**	≥ 22 1
3		$SnCl_4$	15h, -20°C	26 %	**10**	≥ 22 1
4	**9**	BF_3-Et_2O	24h, RT	=	=	
5		$TiCl_4$	24h, -40°C	50 %	**11**	≥ 25 1

a. Determined by ^1H and ^{13}C NMR

Configuration of **10** was assigned as follows NOE effect was observed between H_5 and the C-2' substituents, indicating a (2R) stereochemistry (Fig 2)

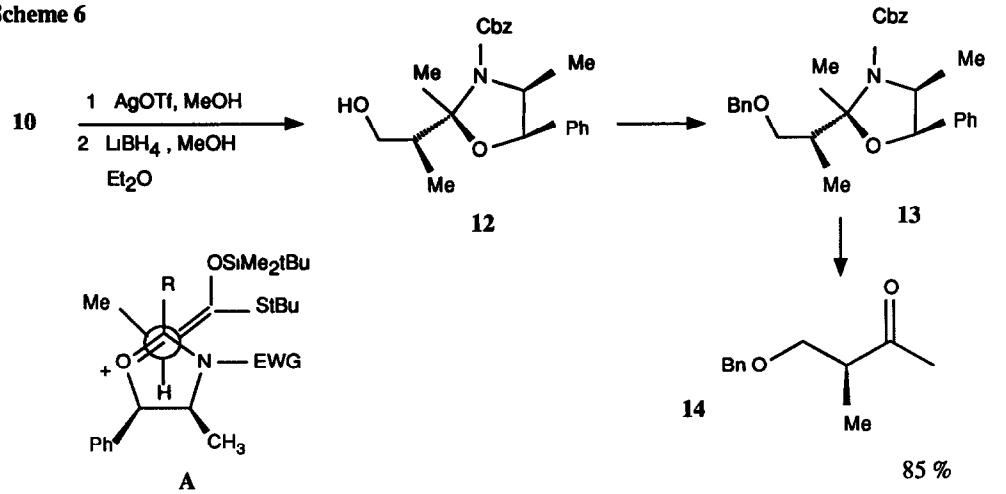
Figure 2



This configuration would result from attack of the nucleophile to the least hindered side of the ring and is in agreement with previous observations [1] Stereochemistry at C-2' was determined by chemical correlation to the known ketone **14**[5] (Scheme 6)

Thiolester **10** was reduced in two steps to the alcohol **12**, which was protected as the benzylether with Ag_2O and benzylbromide Removal of the chiral auxiliary was achieved *via* selective hydrogenation of the carbobenzyloxy group with 5 % Pd-C in wet THF. Hydrolysis of the N-unprotected oxazolidine occured *in situ* to give (S)-ketone **14** in 85 % yield and 90 % optical purity. This result was expected on the basis of the acyclic extended transition structure **A**, which we have previously proposed to be favored for silylenolether addition to **1b** [1]

Scheme 6



In contrast with the behavior observed for silylenolethers and silyketenethiolacetals, the stereoselectivity observed in the addition of the tributylcrotyltin reagent **15**[6] to **2** (Scheme 7) was modest

Scheme 7

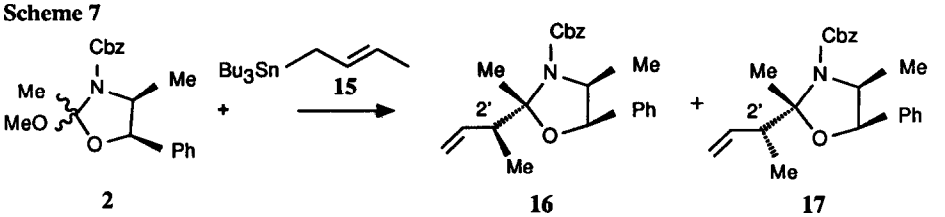


Table 3. Addition of crotyltributyltin **15** to **2**

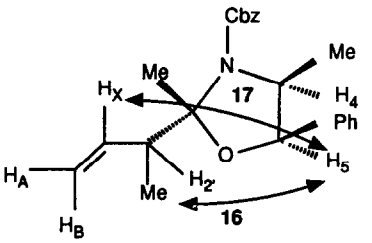
Entry	L A (eq)	Conditions	Yield	**16 : 17**[a]
1	BF_3-Et_2O(2)	4h,-20°C + 2h,-10°C	48%	6 5 1
2		18h, 0°C	80%	5 1
3	$TiCl_4$(2)	6h, -20°C	34%	2 5 1
4	ZnI_2(2.5)	18h, 0°C	10%	3 7 1
5	BF_3-Et_2O(2)	Toluene 18h,0°C	15%	4 1
6		CH_3CN 18h, 0°C	20%	3 1
7	$SnCl_4$(1 5)	18h, 0°C	=	=

a Determined by capillary GC and ^1H- and ^{13}C-NMR spectroscopy

In all the cases studied addition of **15** to **2** results in a mixture of the 2' epimers **16** and **17** with diastereomeric ratios varying from 2 . 1 to 6 : 1 (Table 3) The best result in terms of yield (80 %) and selectivity (5 : 1) were obtained in methylene chloride, using 2 eq of BF_3-Et_2O for one night at 0°C (Table 2, entry 2) Changing the solvent to toluene (entry 5) or CH_3CN (entry 6) is detrimental for yields and does not improve selectivity With $TiCl_4$ both yield and epimeric ratio are rather low (entry 3) In the presence of $SnCl_4$ the cation **5** is probably formed (TLC evidence), but the addition of the tin reagent does not occur and only hydrolysis of the starting material is observed upon aqueous workup (entry 7) This behavior probably originates from ligands methathesis between **15** and $SnCl_4$ which is known to take place at the reaction temperature [7]

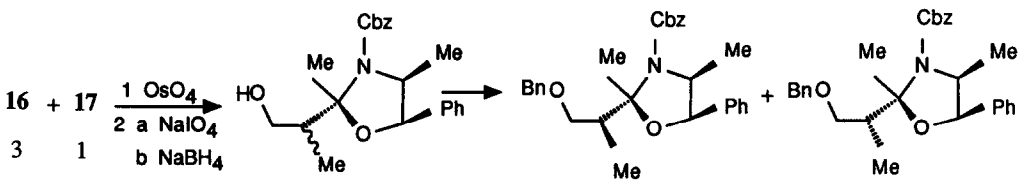
The C2 configuration of **16** and **17** was assigned by NOE difference NMR experiments In both epimers NOE effect was observed between H_5 and the (methyl)allyl side chain (Fig 3), confirming the expected 2R stereochemistry

Figure 3



Stereochemistry at C-2' was determined by correlation to the benzylethers **13** and **18**(Scheme 8)

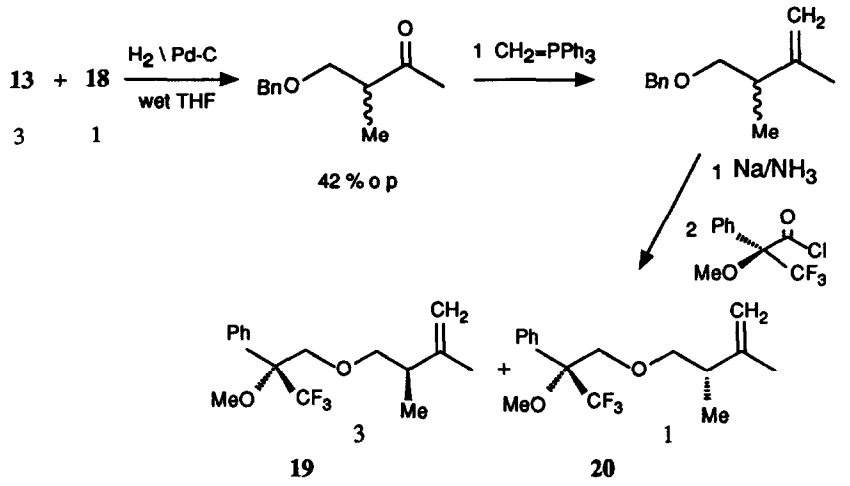
Scheme 8



A 3 1 mixture of **16** and **17** was transformed into the corresponding mixture of epimeric alcohols by Lemieux degradation Protection of the alcohol as the benzylether allowed to identify the major epimer as the same isomer (2' S) **13** obtained *via* silylketeneacetal addition (see scheme 6) This result was rather unexpected, since our formylating agent **1b** had been found to react with **15** with the opposite topicity [1b] Therefore we further confirmed the configuration of **16** by converting **13** and **18** into the known Mosher esters **19** and **20**[5] (Scheme 9)

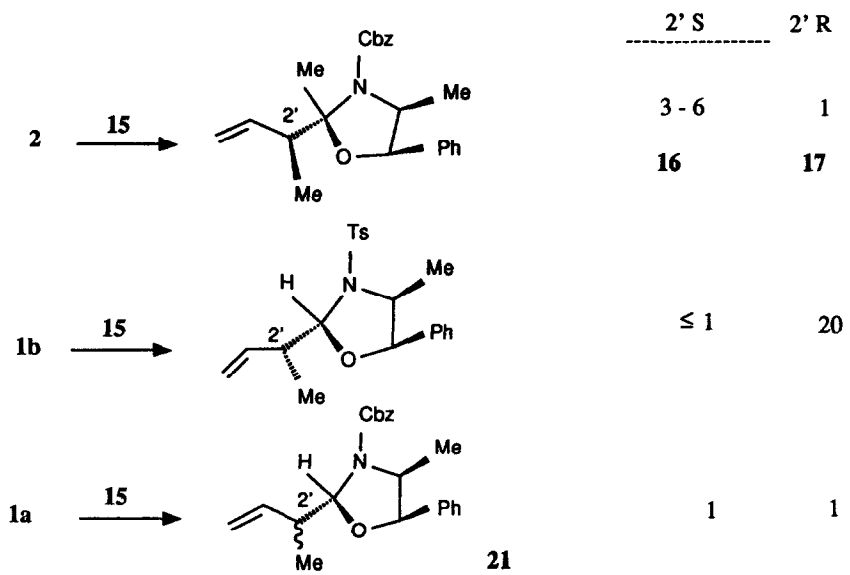
In order to elucidate the factors which determine such an inversion of topicity on going to **1b** to **2**, we performed the same crotyltin addition using the N-carbobenzyloxy protected 2-unsubstitued substrate **1a**

Scheme 9



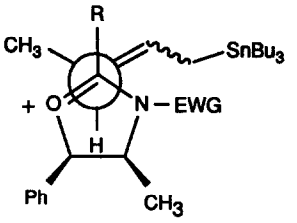
(Scheme 10) The addition of **15** to **1a** in the presence of BF_3-Et_2O gives rise to a 1 1 mixture of 2' epimers It appears therefore that both C-2 alkyl substitution and the nature of nitrogen protecting group have a deep influence on the stereochemical outcome of the addition

Scheme 10 BF_3 mediated addition of crotyltin reagent **15** to oxazolidines **1** and **2**

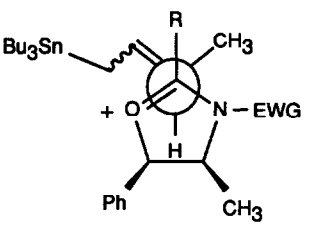


It has been recently stressed[8] that "seemingly small and inconsequential structural changes can have

quite substantial consequences" on the stereochemical outcome of allylstannane (and silane) nucleophilic additions The suggested explanation[8] is that the antiperiplanar (type **B**, leading to the 2'S isomer) and synclinal (type **C**, leading to the 2'R isomer) transition structures for these reactions are inherently close in energy Therefore either pathway can be followed, depending on subtle balances among the substituents



B ⟶ 2'S



C ⟶ 2'R

In summary, norephedrine derived 2-alkoxy-2-methyl oxazolidines have proved to behave as chiral synthetic equivalents of the acyl cation. Acylation of silylketenethiolacetals and silylenolethers appear to be highly diastereoselective, whereas diastereomeric excess up to 73 % could be achieved upon allylation with the stereogenic tin reagent **15**. Removal of the chiral auxiliary can be obtained in high yield and in a single step, *via* catalytic hydrogenation in wet THF Our method compares favorably to the previously reported enantioselective Claisen-type acylations[3] in that norephedrine is commercially available at low price in both enantiomeric forms and in that high stereoselectivities and good yields are achieved under mild reaction conditions

EXPERIMENTAL

^{1}H-NMR spectra were recorded with a Bruker AC-200 or WP-80 or Varian EM-60, while ^{13}C-NMR spectra were recorded with a Bruker AC-200 instrument in the FT mode with tetramethylsilane as internal standard and using $CDCl_3$ or pyridine-d_5 as the solvent. IR spectra were recorded with a Perkin-Elmer 457 spectrophotometer Silica gel 60 F_{254} plates (Merck) were used for analytical TLC, 270-400 mesh silica gel (Merck) for flash chromatography. "Dry" solvents were distilled under N_2 just before use methylene chloride was distilled from CaH_2 All reactions employing dry solvents were run under a nitrogen (from liquid N_2) atmosphere. Melting points are uncorrected All new stable compounds gave satisfactory elemental analysis (C ±0 3%, H ±0 2%, N ±0 2%)

Synthesis of n-carbobenzyloxy-nor-ephedrine

To a solution of N-Cbz-norephedrine (10 g, 66 2 mmol) in H_2O (66 ml) at 0°C were added simultaneously NaOH 2M (36 ml, 73 mmol) and Cbz-Cl (11 3 ml, 79 4 mmol) maintaining the pH around 8 At the end of the addition, the mixture was heated at room temperature and left stirring overnight The mixture was filtered and the white precipitate was washed several times with H_2O After drying under vacuum with P_2O_5, 18 g of Cbz-Nef was obtained Yield 95 %

^{1}H NMR (200 MHz, $CDCl_3$) 1 02 (d, J=6 4, 3H, CH_3-CN), 2 9 (bs, 1H, H-O), 4 1 (m, 1H, H-CN), 4 9 (m, 1H, H-CPh), 4 98 (m, 1H, H-N), 5 14 (s, 2H, CH_2-Cbz), 7 4 (m, 10H,)

Synthesis of 2

To a solution of carbobenzyloxy-norephedrine (500 mg, 1 75 mmol) in dry benzene (12.5 ml, 0 16M) was added trimethylorthoacetate (1.1 ml, 8.35 mmol) A bypassed dropping funnel filled with 4 A molecular sieves was placed between the flask and the reflux condenser and the mixture was refluxed for 10 h before adding pyridinium tosylate (66 mg, 0 26 mmol) After 6 h at reflux the solution was cooled and the solvent evaporated under reduced pressure The crude product was purified by flash chromatography (n-hexane \ AcOEt 85 · 15) affording a 1 1 diastereomeric mixture of oxazolidine **2**. Yield 40 %

2 *^1H NMR* ($CDCl_3$, 300 MHz) 0 8-0.9 (dx2, J=6 4, 3H, CH_3-CN), 1.85-1 95 (mx2, 3H, CH_3-CNO), 3 25-3 4 (m, 3H, CH_3-O), 4 2-4.5 (m, 1H, CH-N), 5 1-5 25 (m, 2H, CH_2-Cbz), 5 55 (d, J=6 5, 1H), 7 4 (m, 10H,)

^{13}C NMR (CD_2Cl_2, 300MHz), selected data 13, 15, 21, 22, 49, 51, 56, 58, 65, 66, 78, 79, 109, 111

Allylation of 2 (Scheme 4, Table 1)

To a solution of **2** (100 mg, 0 29 mmol) in the solvent indicated in table 1 (3 ml, 0 1M) were added sequentially a few 4 A molecular sieves, the nucleophile (XR_3, 0 58 mmol) and the Lewis acid (0 58 mmol) The reactions were run at the temperature and time indicated in table The reactions were quenched with phosphate buffer (pH = 7), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure The crude product was purified by flash chromatography (n-hexane \ AcOEt 9 · 1)

^1H NMR ($CDCl_3$, 200 MHz) 0 8-0 9 (dx2, J=6 4, 3H, CH_3-CN); 1 65-1 75 (sx2, 3H, CH_3-CNO), 2 7-2 9 (bdx2, 2H, CH_2-CH=), 4 2 (mx2, 1H, H-CN), 5.05-5 2 (m, 2H, H_2C=), 5 15-5 25 (m, 2H, CH_2Cbz), 5 23 (d, J=6.2, 1H), 5 75-6 0 (m, 1H, HC=), 7 4 (m, 10H,)

^1H NMR (Py-d_5, 200 MHz, 85°C) 0 97 (d, J=7 1, 3H, CH_3-CN), 1 85 (s, 3H, CH_3-CNO); 3 01 (d, J=J= 6 35, 2H, H_2C-CH=,), 4 09-4 55 (dq, J_{Me-H}= J_{H-H}= 7 1, H-CN), 5 09-5.2 (m, 2H, H_2C=), 5 37 (s, 2H, CH_2-Cbz), 5 5 (d, 1H, J=5 15, H-CO), 5 95-6 15 (m, 1H, J_{Cis}=10, J_{Trans}=17 5, H-C=)

Synthesis of 11

To a solution of **2** (0 16 mmol, 55 mg) and **9** (2 eq) in CH_2Cl_2 (1 ml) a 1 M solution of $TiCl_4$ (1 5 eq) was added at -78°C The reaction was quenched after 24h at -40°C with sat. aqueous KF and extracted with CH_2Cl_2 The crude product was purified by flash chrmatography Yield 50 %

^1H NMR ($CDCL_3$, 200 MHz, 50°C) 0 92 (d, J=5 6, 3H, CH_3-CN), 1 02 (t, J=6 7, 3H, CH_3-CH_2), 1 19 (d, J=7 2, 3H, CH_3-CH), 1 72 (s, 3H, CH_3-CNO), 2 44-2 6 (m, 2H, CH_2-CH_3); 3.46-3 63 (m, 1H, CH-CH_3), 4 3-4 442 (m, 1H, CH-N), 5 1-5.2 (m, 2H, CH_2-Cbz), 5 41 (d, J=5 1, 1H, CH-O), 7 2-7 4 (m, 10H)

^1H NMR (Py-d_5, 200 MHz, 85°C)· 0 92 (d, J=6, 3H, CH_3-CN), 1 1 (t, J=7 5, 3H, CH_3-CH_2), 1 28 (d, J=7 5, 3H, CH_3-CH), 1 95 (s, 3H, CH_3-CNO), 2.6 (q, J=7 5, 2H, CH_2-CH_3), 3 79 (q, J=7 5, 1H, CH-CH_3), 4 5-4 65 (m, 1H, CH-CN), 5 27-5.45 (dd, J=12 5, 2H, CH_2-Cbz), 5 59 (d, J=5 5, 1H, CH-O), 7 3-7 6 (m, 10H)

Synthesis of 10.

To a solution of **2** (0 32 mmol, 110 mg) in CH_2Cl_2 (3 ml, 0 1 M) was added the silylketenethiolacetal (0 64 mmol, 167 mg). The mixture was cooled at -20°C and $TiCl_4$ was added (0 64 mmol). After 15h, the reaction was quenched with phosphate buffer, extracted with CH_2Cl_2 and the solvent evaporated The crude product was purified by flash chromatography (n-hexane \ AcOEt 95 5)

10 *^1H NMR* ($CDCl_3$, 200 MHz) 0.8-0 9 (m, 3H, CH_3-CN), 1 2-1 35 (m, 3H, CH_3-CH), 1 45 (bs, 9H,

tBu-S), 1.8 and 1.9 (sx2, 3H,CH_3-CNO), 3.5-3.62 and 3 68-3.8 (mx2, 1H, CH-CH_3), 4.28-4 55 (m, 1H, CH-N), 5.1-5 25 (m, 2H, CH_2-Cbz); 5.40 (d, 1H, J= 5 8, H-CO), 7.25-7 6 (m, 10H).
^1H NMR (Py-d_5, 300 MHz, 85°C): 0 97 (d, J= 7 1, 3H, CH_3-CN); 1.40 (d, J= 6 4, 3H, CH_3-CH), 1 52 (s, 9H, tBu-S), 2.1 (s, 3H, CH_3-CNO), 3.97 (q, J= 7 1, 1H, H-CCH_3), 4.55 (m, 1H, H-CN), 5 35 (d, 1H, J= 11.4, H-CH-Cbz); 5 41 (d, 1H, J= 11 4, H-CHCbz); 5 61 (d, 1H, J= 7 1, H-CO), 7 25-7 5 (m, 10H)
IR ($CHCl_3$): 1690, 1450, 1400, 1345.

Synthesis of 12

To a solution of **10** (0.25 mmol, 110 mg) in dry THF (2.5 ml, 0.1 M) solid Na_2HPO_4 was added. Then MeOH (0 5 mmol, 0.05 ml) and AgOTf (0 25 mmol, 65 mg) were added sequentially The mixture was refluxed for 2 h during which time MeOH (0 5 mml) and AgOTf (0.25 mmol) were added every 30 min Refluxing was continued for 3h, then the mixture was filtered on a celite pad washing with CH_2Cl_2 and the solvent was evaporated. The crude product was purified by flash chromatography (n-hexane \ AcOEt 9 1) Yield 65 %

^1H NMR ($CDCl_3$, 200 MHz). 0.82 (d, J= 6 5, 3H, CH_3-CN), 1 28 (d, J= 7 3, 3H, CH_3-CH); 1 87 (s, 3H, CH_3-CNO), 3 4 (q, J= 7.3, 1H, H-CCH_3); 3.65 (s, 3H, CH_3-O), 4 32 (m, 1H, H-CN), 5 1 (d, J= 12, 1H, H_A-Cbz); 5.2 (d, J= 12, 1H, H_B-Cbz); 5.56 (d, J= 5.7, 1H, H-CO), 7.2-7.6 (m, 10H)
^1H NMR (Py-d_5, 200 MHz, 85°C). 0.93 (d, J= 6 35, 3H, CH_3-CN), 1 37 (d, J= 7 3, 3H, CH_3-CH), 2 08 (s, 3H, CH_3-CNO); 3 68 (s, 3H, CH_3-O), 4 53 (m, 1H, H-CN), 5 3 (d, J= 12 5, 1H, H-Cbz), 5 41 (d, J= 12 5, 1H, H-Cbz); 5.57 (d, J= 5.75, 1H, H-CO); 7 2-7 6 (m, 10H).

To a solution of the methylester (0.16 mmol, 60 mg) in Et_2O (1 5 ml, 0 1 M) $LiBH_4$ (0 32 mmol, 6 mg) and MeOH (0 01 ml, 0.24 mmol) were added and the mixture was refluxed for 2h The reaction was quenched by careful addition of HCl 0 5 % whilst cooling in an ice bath Extraction with CH_2Cl_2 and evaporation of the solvent yielded an oil from which alcohol **12** was isolated in 76 % yield by flash chromatography (n-hexane \ AcOEt 65 35)

12 *^1H NMR* ($CDCl_3/D_2O$, 200 MHz) 0.82 (d, J=6.5, 3H, CH_3-CN); 1 15 (d, J=7, 3H, CH_3CH), 1 58 (s, 3H, CH_3-CNO); 2 4-2 7 (m, 1H); 3 4 (m, 1H), 4 05 (bd, 1H), 4 35 (m, 1H, H-CN), 5 2 (d, 2H, J=5, CH_2Cbz); 5 4 (d, J=5 5, 1H, H-CO); 7 2-7.5 (m, 10H)
IR ($CHCl_3$) 3520, 1690, 1490, 1450, 1400

Synthesis of 13.

To a solution (0 16 M) of the alcohol **12** in Et_2O was added $PhCH_2Br$ (1 5 mmol) and Ag_2O (1 2 mmol) The mixture was refluxed for 6 h and then was filtered on a celite pad washing with Et_2O The solution was dried with Na_2SO_4 and the solvent evaporated under reduced pressure The crude product was purified by flash chromatography (n-hexane AcOEt 92 8) Yield 76 %

13 *^1H NMR* (Py-d_5, 200 MHz, 85°C) 0 92 (d, J= 6 5, 3H, CH_3-CN), 1 2 (d, J= 7 0, 3H, CH_3-CH), 1 95 (s, 3H, CH_3-CHO), 3 2 (m, 1H, H-CCH_3), 3 5-3 62 (m, 1H, H-OCH_2Ph), 4 0 (dd, J= 5, J= 15, 1H, H-OCH_2Ph), 4 45-4 65 (m, 1H, H-CN), 4 58 (s, 2H, CH_2-Ph), 5.36 (dx2, J= 10 2, 2H, CH_2-Cbz), 5 55 (d, J= 5, 1H, H-CO), 7 2-7 6 (m, 15H)
^{13}C NMR (Py-d_5, 300 MHz, 85°C) Selected data· 14 14 (CH_3-CH), 16.44 (CH_3-CN), 25 84 (CH_3-CNO), 40 97 (CH-CH_3), 56 38 (CH-N), 66 61 (CH_2-Cbz), 72 45 and 72 70 (O-CH_2-Ph and CH_2-OBn), 80 70 (CH-O)

Synthesis of 14

To a solution (0 03 M) of **13** in wet THF was added 5% Pd/C and the mixture was stirred under a H_2

atmosphere for 30 min The crude was filtered on a celite pad which was washed with CH_2Cl_2 and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane \ AcOEt 85 : 15). Yield 85 %.

14. *^1H NMR* ($CDCl_3$, 200 MHz). 1.15 (d, J=5.5, 3H, CH_3-CH); 2.2 (s, 3H, CH_3-CO); 2 9 (m, 1H) , 3.5 (dd, J=6 5 and J=5, 1H), 3 68 (dd, J=J=6.5, 1H), 4 5 (s, 2H, CH_2Cbz), 7 3-7 6 (m, 5H)
^{13}C NMR ($CDCl_3$), selected data 13, 28, 47, 72, 73.
$[\alpha]_D$= +16 (c2, $CHCl_3$)

Methallylation of 2 (Scheme 7, Table 3)

To a solution of **2** (100 mg, 0 29 mmol) in the solvent indicated in table 3 (3 ml, 0.1 M), tributylcrotyltin (0.58 mmol) and the Lewis acid (0.58 mmol) were added. The reactions were run at the temperature and time indicated in the table and in the presence of 4 A sieves The reactions were quenched with phosphate buffer (pH = 7), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure The crude product was purified by flash chromatography (n-hexane \ AcOEt 95 5)

16 and **17** *^1H NMR* ($CDCl_3$, 200 MHz) 0 79-0.9 (mx2, 3H, CH_3-CN), 1 0-1 02 (mx2, 3H, CH_3-CH); 1 55-1 78 (mx2, 3H, CH_3-CNO), 3 0-3.12 and 3 28-3 42 (m, 1H, H-CCH_3); 4 2-4 5 (m, 1H, H-CN); 4 9-5 13 (mx2, 2H, H_2C=); 5 15-5 28 (m, 2H , H_2C-Cbz), 5 32-5.47 (dx2, J=5 2, 1H, HC-O), 5 79-6 06 (mx2, 1H, HC=); 7.2-7.5 (m, 10H,)
^{13}C NMR (Py-d_5, 85°C, 200 MHz) Selected data 47.6 (CHN), 67 7 (CH_2-Cbz), 81 9 (CHO); 97 7 (CNO), 116.5 (CH_2=), 127 3 (CH=).

16 *^1H NMR* (Py-d_5, 300MHz, 85°C) 0 95 (d, J=6 5, 3H, CH_3CN), 1 16 (d, J=7, 3H, CH_3-CH), 1 85 (s, 3H, CH_3-CNO), 3 5 (m, 1H, HC-CH_3), 4 6 (dq, $J_{Me\text{-}H}$=$J_{H\text{-}H}$=6 5, H-CN), 5 05-5 25 (m, 2H, H_2C=), 5 38 (d, J=4.2, 2H, CH_2-Cbz); 5 57(d, J=5.55, 1H, H-CO), 7 01-7 19 (m, 10H)

17 *^1H NMR* (Py-d_5, 300MHz, 85°C) 0 92 (d, J=6 5, 3H, CH_3-CN), 1 25 (d, J=7, 3H, CH_3-CH), 1 85 (s, 3H, CH_3-CNO), 3.5 (m, 1H, H-CCH_3), 4 48-4 52 (m, 1H, H-CN), 5 05-5 25 (m, 1H, CH_2=), 5 32 (d, J=4 2, 1H), 5 55 (d, J=5 5, 1H), 7 01-7 19 (m, 10H).

Dihydroxylation of 16 and 17 Synthesis of 13 and 18

The dihydroxylation was effected on a diastereomeric mixture of **16** and **17** according to the following procedure To a solution (0 05 M) of the substrate (1 mmol) in acetone\ H_2O (8 : 1) at room temperature a solution of OsO_4 (0 1 mmol, 0 7868 M in tBuOH) and Me_3NO H_2O (2 mmol) were added After 4 h the reaction was quenched with a satured solution of Na_2SO_3, extracted with AcOEt, washed with brine and dried with Na_2SO_4 The resulting crude mixture of diols was used in the next reaction A pure sample could be obtained for analytical purposes by flash chromatography (n-hexane \ AcOEt 4 . 6). Yield 88 %

^1H NMR ($CDCl_3/D_2O$, 200 MHz, 4 diastereoisomers)· 0 8 (d, J=6 5, 3H, CH_3-CN); 1.0 (d, J=6 9, 3H, CH_3-CH), 1 7-1 9 (sx2, 3H, CH_3-CNO), 2 5-2 9 (mx2, 1H, H-CCH_3), 3 45-3 6 (m, 1H, H_A), 3 7-3 9 (m, 1H, H_B), 3 95-4 1 (m, 1H, H_X), 5 15-5 25 (m, 2H, CH_2-Cbz); 5 35 (m, 1H, H-CN), 5 35-5 45 (m, 1H, H-CO)

To a solution of the diol (0 04 M, 1 mmol) in dioxane \ H_2O (4 1) $NaIO_4$ (1 5 mmol) was added at room temperature and the mixture stirred for 1 h before adding $NaBH_4$ (3 mmol) After 1 h the reaction was quenched cautiously with NH_4Cl, repeatedly extracted with AcOEt, dried with Na_2SO_4 and the solvent evaporated under reduced pressure The crude product was purified by flash chromatography (n-hexane-AcOEt 65 35), to give a 3 1 mixture of alcohol **12** and its 2' epimer in 88% yield Such a

mixture was directly submitted to benzylation as described for **12** (see above), and a 3:1 mixture of benzylethers **13** and **18** was isolated in 75% yield. Spectral characterization of **13** was reported above.

13 and **18:** *^{1}H NMR* ($CDCl_3$, 200 MHz): 0.7-0.9 (m, 3H, CH_3-CN); 1.0-1 2 (m, 3H, CH_3-CH); 1.7-1.9 (m, 3H, CH_3-CNO); 2.65-2.85 and 2.9-3.1 (mx2, 1H, H-CCH_3); 3.3-3.5 (m, 1H), 3.6-3.7 and 3.8-3.9 (mx2, 1H), 4 35 (m, 1H, H-CN); 4.5 (m, 2H, H_2-CPh); 5.1-5.35 (m, 2H, H_2-CCbz); 5.4 (d, J= 5.75, 1H, H-CO); 7 2-7 5 (m, 15H).

IR ($CHCl_3$): 1690, 1600, 1490, 1450, 1400, 1350

18: *^{1}H NMR* ($CDCl_3$, 200 MHz). 0.92 (d, J= 6.5, 3H, CH_3-CN), 1.3 (d, J= 7, 3H, CH_3-CH), 1.9 (s, 3H, CH_3-CNO), 3.2 (m, 1H, H-CCH_3); 3.5-3.62 (m, 1H); 3.8 (dd, J= 5 and J= 15, 1H); 4 45-4 65 (m, 1H, H-CN); 4 52 (s, 2H, CH_2-Ph), 5 36 (d.2, J= 10.2, 2H, CH_2-Cbz); 5.45 (d, J= 5, 1H, H-CO); 7 2-7 6 (m, 15H)

^{13}C NMR (Py-d_5, 300 MHz, 85°C) Selected data : 13.06 (CH_3-CH); 15.37 (CH_3-CN); 27 28 (CH_3-CNO), 40 97 (CH-CH_3); 56 38 (CH-N); 67.15 (CH-Cbz), 72.45 and 72 70 (O-CH_2-Ph and CH_2-OBn); 80.70 (CH-O).

Methallylation of 1a Synthesis of 21

To a solution of **1a** (0 2 mmol) and tributylcrotyltin (0.4 mmol) in dry CH_2Cl_2 (2 ml), BF_3Et_2O (0 4 mmol) was added at -78°C. After 1h at -78°C the reaction was quenched with phosphate buffer and extracted with CH_2Cl_2. Evaporation of the solvent and purification by flash chromatography (9 1 hexane·AcOEt) gave **21** as a 1 1 epimeric mixture in 75% yield.

21: *^{1}H NMR* (Py-d6, 200MHz, 60°C): 0.88 (d, J=6.6Hz, 3Hx2); 1 15 (d, J=6.7Hz, 3H); 1 25 (d, J=6.7Hz, 3H); 3 25-3 45 (m, 1Hx2); 4 35-4 45 (m, 1Hx2, CHN), 5.05-5.25 (m, 2Hx2, CH_2=); 5 32 (m, 2Hx2, CH_2C=O), 5 5 (d, J=5.8Hz, 1Hx2, PhCHO); 5 5 (d, J=5.5 Hz,1H, CH(O)N); 5 6 (d, J=5.8Hz, 1H, CH(O)N); 5.90-6 12 (m, 1Hx2), 7 2-7.5 (m, 5Hx2)

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