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New Synthetic Approaches to the Oxahydrindane Subunit of Avermectins.

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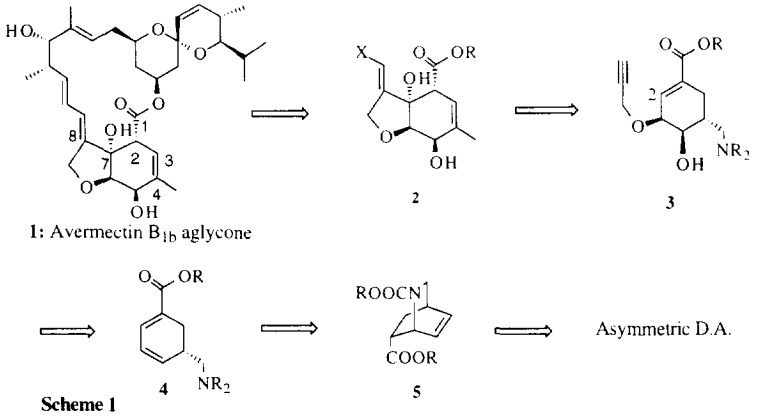
Abstract: Isoquinuclidine derivatives **9a**, **9b**, resulting from an asymmetric Diels-Alder cycloaddition, afforded, after a two step sequence of reactions, functionalized cyclohexenes **11** and **31** precursors of the oxahydrindane subunit of Avermectins. © 1997 Elsevier Science Ltd.

Avermectin antibiotics[1], extracted from *Streptomyces avermitilis*, exhibit highly potent antiparasitic properties. Their original structure as well as their biological activity stimulated a lot of synthetic studies[2] culminating with several total syntheses[3]. In connection with the synthesis of the spiroketal subunit of these antibiotics[4] and an other synthetic approach[5], it appeared that isoquinuclidine derivatives **5**, resulting from a stereoselective Diels-Alder cycloaddition[6], could well be good candidates for the developpment of a new strategy in the synthesis of oxahydrindane moiety of Avermectins[7]. Our retrosynthetic analysis was founded on a fragmentation[8] of the [2,2,2]-azabicyclic system in **5** and on a stereoselective dihydroxylation which should give rise to cyclohexene derivative **3**. After oxidation at C2, elimination of the nitrogen functionality, a radical cyclisation already described by Julia[3d] could afford the target bicyclic derivative **2** (Scheme 1). Our preliminary results concerning this strategy are presented there in.



1: Avermectin B_{1b} aglycone

2 **3** **4** **5**

Scheme 1

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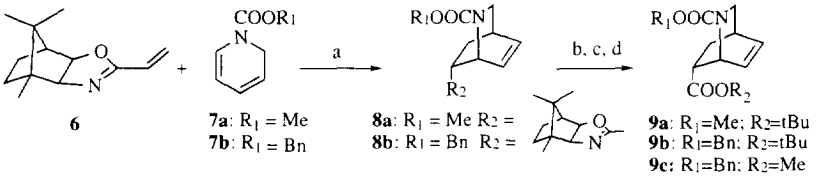
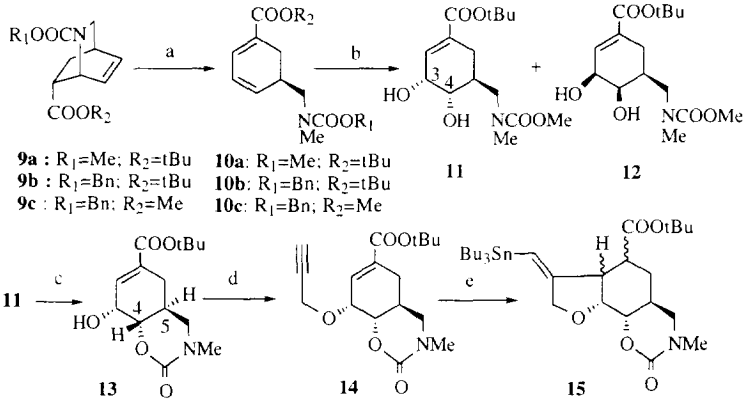
As previously described[6], isoquinuclidine derivatives **8a** and **8b** were obtained respectively in 60% and 45% yields with a diastereoselective excess of 90%. A two step hydrolysis of the oxazoline ring afforded the corresponding carboxylic acids which in turn led to the *tert*butyl esters **9a** and **9b** in respectively 63 and 58% overall yields (Scheme 2).



Scheme 2 : a) TFAA (3 eq.), Propylene oxide (6 eq.), **7a** or **7b** (5 eq.), CH_2Cl_2, -78°C, 3h. b) Na_2CO_3 (2.2 eq), $ClCO_2R_1$ (1.1 eq.), CH_2Cl_2, 20°C, 6 h. c) NaOH (1M), MeOH, 60°C, 3h. d) Me_2CCH_2, H_2SO_4, CH_2Cl_2, 20°C, 15h.

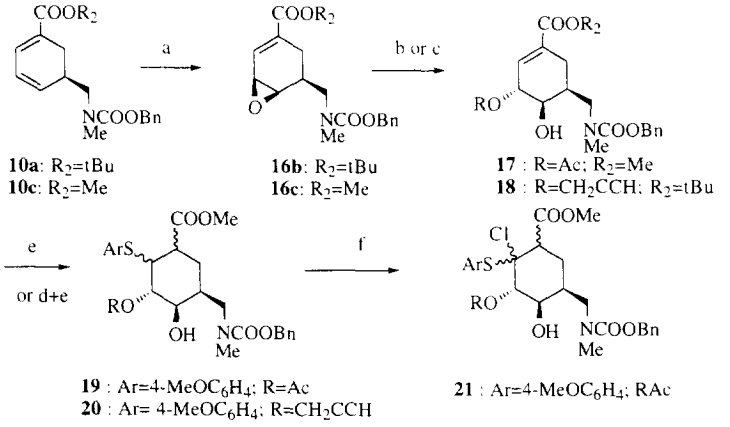
Deprotonation of ester **9a** with LiHMDS induced a fragmentation of the C-N bond[8]. The resulting cyclohexadiene derivative **10a** was isolated in 89% yield after quenching of the lithium amide intermediate with methyl iodide. Dienic ester **10a** was in turn submitted to a regioselective dihydroxylation[9]. Best results were obtained with AD-mix-β which afforded a mixture of diols **11** and **12** in 29 and 18% yield respectively[10]. Despite this lack of stereoselectivity, the synthesis proceeded with diol **11** as a model. The presence of a carbamate unit allowed an internal protection for the alcohol at C4. Thus, after treatment with LiHMDS, the bicyclic oxazinone derivative **13** was isolated in 45% yield[11]. Classical propargylation afforded compound **14** (66%) which was subsequently subjected to the Bu_3SnH/AIBN-promoted radical cyclisation reaction giving rise to the expected oxahydrindane derivative **15** as a mixture of diastereoisomers in 53% yield (Scheme 3).



Scheme 3 : a) 1 : LiHMDS (2eq.), THF,-40°C to 20°C; 2 : MeI (30 eq.), 20°C, 15h. b) AD-mix-β (1.4 g/mmol), H_2NSO_2Me (1.5eq.), tBuOH-H_2O (50:50), 20°C, 20h. c) LiHMDS (2 eq.) THF, 0°C to 40°C, 20h. d) LiHMDS (1.5 eq.), $BrCH_2CCH$ (1.5eq.), DMF, -40°C to 20°C, 4h. e) Bu_3SnH (2 eq.), AIBN (cat.), PhMe, Rfx., 3h.

The lack of stereoselectivity during the dihydroxylation step, let us to consider other tactics to functionalize the C3-C4 double bond[12]. Accordingly oxidation of compound **10** with *m*CPBA afforded quantitatively epoxide **16** as single isomer. As observed earlier[13], homoallylic carbamate directed a diastereofacial epoxidation through an hydrogen bonded transition step. Nucleophilic opening of epoxidic moiety was achieved under two sets of condition. Acetic acid in the presence of neutral alumina[14], afforded acetate derivative **17** in 44% yield, with 6% of the regioisomeric diol, whereas the propargylated derivative **18** (Yield 45%) resulted from a ring opening mediated by CAN in the presence of propargylic alcohol[15,16] (Scheme 4).

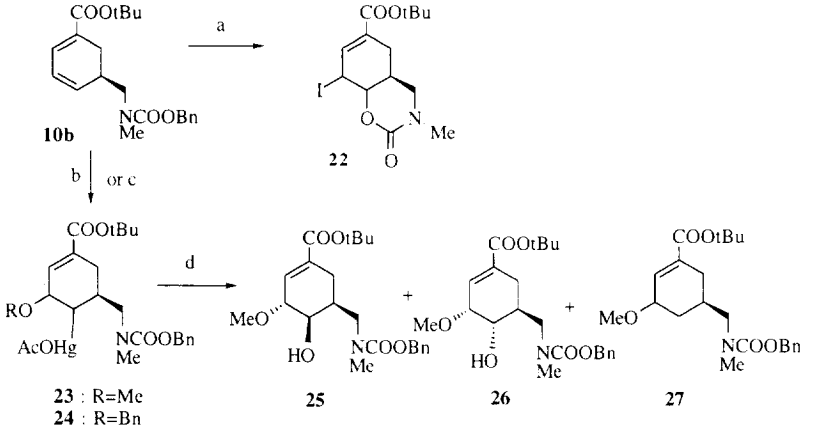
The possible oxidation at C2 was then studied at this stage. In our initial retrosynthetic analysis, introduction of a carbonyl group equivalent in this position could be achieved by a Pummerer oxidation. This type of functionalization has been already described by Bartlett [17]. However, in our case conjugate addition of 4-methoxythiophenol needed acidic methanolysis of *tert*-butyl ester and excess of base and nucleophile. Under these forcing conditions thioethers **19** and **20** were obtained in 62 and 69% yield respectively. According to Bartlett [17] treatment of these compounds with sulfuryl chloride afforded chlorothioether **21** in 48% yield (Scheme 4). But compound **21**, under hydrolytic conditions, didn't lead to the expected β-ketoester.



Scheme 4: a) *m*CPBA (1.2eq.), CH_2Cl_2, 20°C, 1h. b) AcOH, Al_2O_3, 20°C, 20h. c) $HCCCH_2OH$, CAN, CH_2Cl_2, 20°C, 20h. d) MeOH, HCl. e) LiHMDS (4eq.), $4\text{-}MeOC_6H_4SH$ (3-5eq.), THF, 20°C, 20h. f) SO_2Cl_2 (7eq.), CH_2Cl_2, 0°C, 2h.

This approach which included a nucleophilic opening of epoxide, afforded compounds with a *trans* relationship between oxygens at C3 and C4 which has to be further corrected *via* an oxidation-reduction sequence at C4[18] To preclude these additonal steps, two other functionalizations of the C3-C4 double bond have been studied. Thus, iodo carbamoylation of compound **10b** afforded iodo derivative **22** in 65%

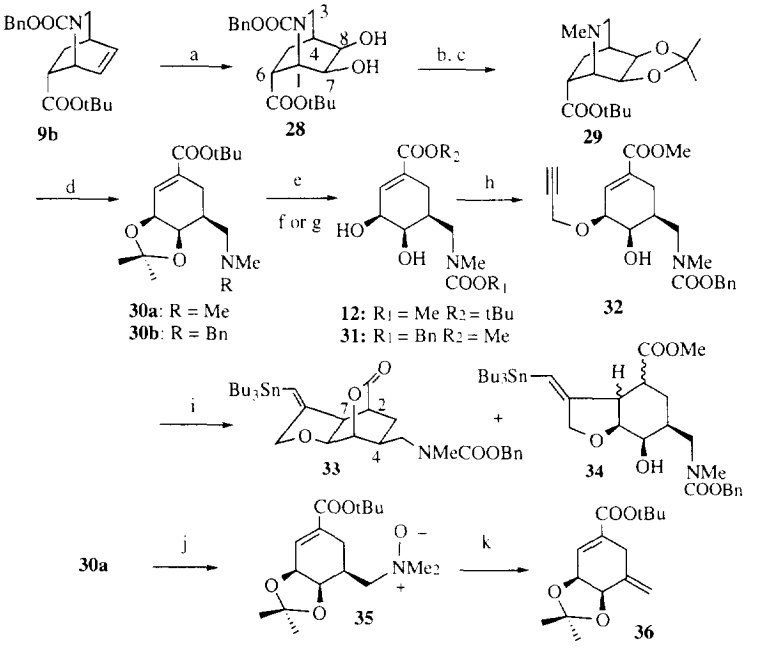
yield. However, coupling constant between C3-H and C4-H in this compound was too small to allow stereochemical asignments at these centers. Furthermore, nucleophilic displacement with propargylic alkoxide or other nucleophiles led mainly to aromatized derivatives. On the other hand, mercuric salt induced cyclisation, gave rise to compounds **23** or **24** in 73 and 77% yields respectively. The intramolecular nucleophilic displacement was in these compounds overcome by the intermolecular pathway involving the solvent. Homolytic cleavage of the carbon mercury bond with concomitant quenching with oxygen afforded the expected methoxy alcohol derivative **25** (33%), epimeric compound **26** (20%) and trace amount of **27** (Scheme 5). Stereochemical assignments in **25** and **26** were attributed after cyclisation affording oxazinone derivatives by comparison with compound **13**.



Scheme 5 : a) I_2 (1.5eq.), CH_2Cl_2, 20°C, 6h. b) $Hg(OAc)_2$ (2eq.), MeOH, 20°C, 24h. c) $Hg(OAc)_2$ (2eq.), BnOH, 20°C, 10h. d) $NaBH_4$, O_2, DMF, 4h.

The lack of stereoselectivity during the dihydroxylation of dienic esters **10** let us to examine a modification of our initial scheme in which this reaction could be performed before the fragmentation. Therefore isoquinuclidine derivative **9b** under classical dihydroxylation conditions afforded a single diol derivative **28** in 90% yield. After protection of the diol moiety, the resulting acetonide was subjected to a three step one pot sequence of reactions. Namely, hydrogenolysis of the Cbz group, imminium formation by nucleophilic attack of the secondary amine on formaldehyde and reduction of the transcient imminium intermediate. The *N*-methyl isoquinuclidine **29** was thus isolated in 92% yield. *N*-alkylation with benzyl bromide or methyl iodide was followed by a Hofmann elimination affording compounds **30a** and **30b** in 84% overall yields[18](Scheme 6). In order to take advantage as previously of an internal protection of alcohol at C4, compound **30b** was subjected to an acylative cleavage of the *N*-benzyl group in the presence of benzyl chloroformate giving rise, after acidic hydrolysis of the acetonide and transesterification to the diol urethane **31**[20] in 82% yield. Surprisingly, basic treatment of this compound did not afford the *cis*

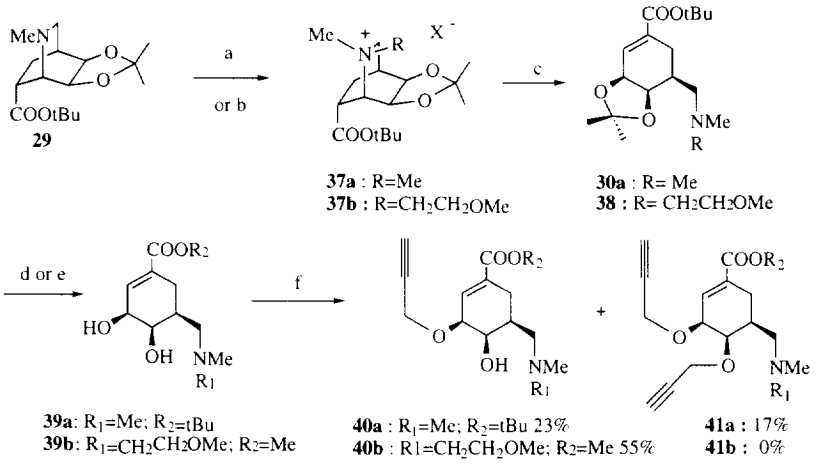
bicyclic oxazinone derivative as in the *trans* series. Fortunately, after double deprotonation, a regioselective alkylation of alcoholate at C3 occured in the presence of propargyl bromide leading to compound **32**[12] in 65% yield with 10% of starting material. This regioselective reaction can well be due to an internal chelation between alcoholate at C4 and the side chain urethane functional group (*vide infra*). Radical induced cyclisation[3d] afforded compound **33** in 90% yield and in 40% overall yield from **9b**. Trace amounts of ester **34** was also isolated (Scheme 6). The spontaneous lactonisation affording **33** allowed to attribute the configurations at C2 and C7 in this molecule[21]. Introduction of the methylenic side chain as precursor of the C3-C4 double bond[21]has been also studied on compound **30a**. Accordingly, oxidation of **30a** afforded the expected *N*-oxide **35** which was in turn thermolyzed affording (by a Cope elimination) compound **36** in 50% yield (Scheme 6).



Scheme 6 : a) OsO_4 (0.02 eq.), NMO (1.5 eq.), H_2NSO_2Me (1.5 eq.), MeCOMe, 20°C, 4 h. b) $Me_2C(OMe)_2$, PTSA (0.1 eq.). c) H_2, Pd-C (10%), HCHO-H_2O (exc.), MeOH, 20°C, 2h. d) MeI (exc.) or BnBr (exc.), 20°C, 3h. tBuOK (1.2eq.),THF, 20°C, 1h. e) **30a**: $ClCO_2Bn$ (1.2eq.), PhMe, 50°C, 2h. **30b**: $ClCO_2Bn$ (1.2eq.), PhMe, 20°C, 4h. f) HCl (sat.), MeOH, 20°C, 2h. g) TsOH (1.2eq.), tBuOH, 60°C, 20h. h) LiHMDS (2 eq.), $BrCH_2CCH$ (1.1 eq.), DMF, 0°C to 20°C, 3h. i) Bu_3SnH (2 eq.), AIBN (cat.), PhMe, Rfx., 3 h. j) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 2h. k) $C_6H_5CH_3$, 110°C, 2h.

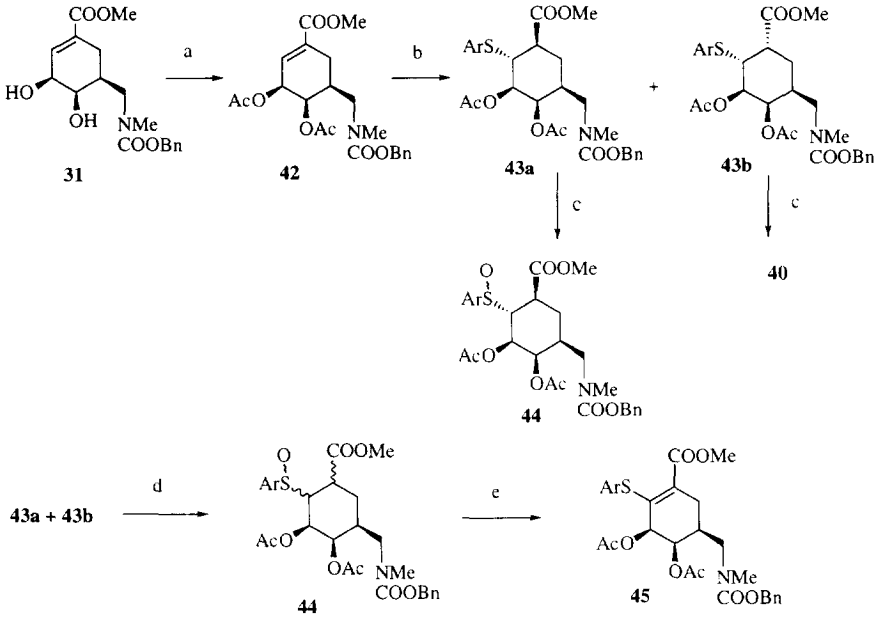
In the preceeding synthesis, nitrogen has to be alternatively used as an urethane or a free amino group in a sequence of four reactions albeit in good overall yield. In order to develop a more

straightforward sequence, the direct use of a tertiary amine has also been studied. Thus, quaternarisation of isoquinuclidine derivative **29** with methyl iodide or methoxyethylbromide afforded respectively the quaternary ammonium salts **37a** (95%) or **37b** (40%). Hofmann elimination followed by acetonide hydrolysis gave rise to diols **39a** or **39b**. Propargylation of these compounds gave striking results. With the dimethylamino derivative **39a** a mixture of the two *O*-alkylated regioisomers **40a** and **41a** was obtained. Whereas a regioselective *O*-alkylation was observed with compound **39b** in which a chelation between the alcoholate at C4 and the methoxyethyl side chain can be involved, the monopropagylated derivative 40 b being isolated in 55% yield (Scheme 7).This result also confirms the previous hypothesis of related chelated intermediate during alkylation of urethane **31** (Scheme 6).



Scheme 7: a) $BrCH_2CH_2OMe$ (2eq.), Bu_4NI (1eq.), CH_2Cl_2, 20°C, 4h. b) MeI (exces), 20)C, 3h. c) t-BuOK (1.2eq.), THF, 20°C. d) MeOH, HCl, 20°C, 6h. e) PTSA (1.2eq.), tBuOH, 60°C, 20h. f) LiHMDS (2eq.), $BrCH_2CCH$ (1.1eq), DMF, 0°C. 3h.

Oxidative functionalisation at C2 was also studied in this series. Compound **31** in which all substituents are in a *cis* relationship gave unexpected results. After protection of the diol moiety, conjugate addition gave a separable mixture of *trans* and *cis* isomers **43a** and **43b** (2.5:1, 90%). Oxydation of these thioethers with sulfurylchloride afforded respectively sulfoxide **44** (73%) and starting material **42** (66%) (Scheme 8). The formation of this later compound can be explain by the *trans* relationship between hydrogen at C1 and sulfur oxidized intermediate at C2 allowing an easy elimination reaction. Formation of sulfoxide **44** is the result of a nucleophilic substitution on sulfur during work up. This peculiar behaviour contrasts with the reactivity observed in the *trans* series (Scheme 4). The Pummerer oxidation was also studied on the mixture of sulfides **43a-43b**. Oxidation with *m*CPBA oxydation afforded a diastereomeric miture of sulfoxide **44** in 85% overall yield. Treatment of this compound with trifluoroacetic anhydride gave directly the thioenolether **45** in 56% yield. However,this compound in which the thioenolether is conjugated with the ester group proved to be quite resistant to hydrolysis.



Scheme 8: a) Ac_2O, C_5H_5N, DMAP, CH_2Cl_2. b) 4-$MeOC_6H_4SH$ (4eq.), LiHMDS (4eq.), THF, 20°C. c) SO_2Cl_2, CH_2Cl_2, 0°C, 2h. d) *m*CPBA, CH_2Cl_2, 0°C, 0.5h. e) TFAA (2.1eq.), 2,6-MeC_5H_3N (1eq.), CH_2Cl_2, 20°C, 2h.

In conclusion, several synthetic approachs to the oxahydrindane subunit of Avermectins have been studied[22]. Two advanced intermediates lacking a tertiary hydroxy group at C7 were prepared. Peculiarly, compound **33** was obtained in high overall yield. The feasibility of elimination of the nitrogen moiety has been also examined. The different routes to introduce the correct functionalization at C7 gave for the moment various results depending of the relative configurations of substituents. Further synthetic studies directed toward the fully functionalized oxahydrindane subunit of Avermectins are under current development.

Experimental

All melting points are uncorrected. ^1H NMR spectra were taken on 200 and 250 MHz instruments and are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet), integration, coupling constants in hertz. ^{13}C NMR were taken at 50 and 62.5 MHz. Solvents and reagents were dried and purified prior to use when deemed necessary. THF and diethyl ether were distilled from sodium metal-benzophenone; dichloromethane, pyridine, triethylamine and diisopropylamine were distilled from calcium hydride; hexamethylphophoric triamide, dimethylformamide,

were distilled from calcium hydride and stored on 4Å molecular sieves. Usual work up means that organic layers were dried over magnesium sulfate, filtrated and evaporated *in vacuo*.

Asymmetric Diels-Alder reaction. Preparation of adduct **8b**.To a stirred solution of oxazoline **6**[6] (2.193 g, 10.7 mmol), propylene oxide (4.5 mL, 6 equiv.) and trifluoroacetic anhydride (4.6 mL, 3 equiv.) in anhydrous dichloromethane (25 mL), under argon at - 78°C, was added dropwise a solution of dihydropyridine **7b** (1.015 g, 5 equiv.) in dichloromethane (50mL). The resulting mixture was stirred for additional 3 hours at the same temperature and poured into an aqueous solution of sodium hydrogencarbonate (5%, 25 mL). After usual work up and purification by column chromatography (Pentane/AcOEt: 20:80) afforded adduct **8b** (1.935 g, 43%).

Compound **8b** : $[\alpha]_D^{20}$ -112.5 (c 1.58, $CHCl_3$). IR ($CHCl_3$) : 3040, 3000, 2960, 2880, 1690, 1650. ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 5H, Arom.), 6.49 (m, 2H, C7'H, C8'H), 5.14 (2H, d, $PhCH_2O$, J = 11 Hz), 5.06 (m, 1H, C1'H), 4.37 (d, 1H, C7aH, J = 8 Hz), 3.76 (2d, 1H, C3aH, J = 8 Hz), 3.30 (br. d, 1H, C3'H, J = 9.5 Hz), 3.01 (br. d, 1H, C3'H, J = 9.5 Hz), 2.80 (m, 2H, C4'H), 2.92 (m, 1H, C6'H), 2.07 (d, 1H, C7H, J = 5 Hz), 1.96 (m, 1H, C5'H), 1.72 (m, 2H, C5'H, C6H), 1.47 (m, 1H, C6H), 0.94 (m, 2H, $C5H_2$), 1.01, 0.84, 0.81 (3 x 2s, 3 x 3H, 3 CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.7 (C2), 155.8 (NC=O), 136.8, 128.4-127.8, 127.6 (Arom.), 134.2, 131.1 (C7' et C8'), 86.8 (C7a), 80.6 (C3a), 66.7 (Ph-CH_2-O), 48.6-46.7 (C4, C8, C3',C1', C7), 38.9 (C6'), 34.1 (C5), 30.5 (C4'), 27.3 (C6), 23.3 (CH_3), 18.9 (CH_3), 11.5 (CH_3), 23.2 (C5'). MS (DIC, NH_3) : *m/e* 421 $[M+H]^+$.

Preparation of compound **9b**. A mixture of adduct **8b** (1.935 g, 4.54 mmol), benzyl chloroformate (771µL, 1.2 equiv) in dichloromethane (10 mL) and sodium carbonate (1.042 g, 2.2 equiv.) in water (25 mL) was vigorously stirred at 20°C for 6 hours. After usual work up and column chromatography (Pentane/AcOEt: 40:60) ester urethane intermediate was isolated (2.496 g, 96%).

A solution of ester urethane intermediate (2.434 g, 4.25 mmol) in methanol/aqueous sodium hydroxide (2.5 M, 2/1) was heated for 12 hours at 80°C. The reaction medium was partitioned between dichloromethane and water. Aqueous layer was washed with dichloromethane and the resulting organic layers were extracted with an aqueous solution of sodium carbonate. The aqueous phases were acidified with hydrochloric acid (2N) and extracted three time with ether. After usual work up organic phases were evaporated *in vacuo* and the resulting residue in solution in dichloromethane (15mL) with catalytic amount of sulfuric acid, was treated at 0°C by a steam of isobutene. After stirring at 20°C for 24 hours , the dichloromethane solution was concentrated *in vacuo* to 7mL and treated with a saturated solution of sodium carbonate. After usual work up, the crude residue was purified by column chromatography on silica gel (Pentane/AcOEt: 85:15) affording **9b** (846 mg, 58%).

Compound **9b** : $[\alpha]_D^{20}$ -97.3 (c 1.11, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (m, 5H, Arom.), 6.40 (m, 2H, C7H, C8H), 5.15-5.10 (m, 3H, $PhCH_2O$, C1H), 3.30 (dd, 1H, C3H, J = 10, 2.5 Hz), 3.00 (m, 2H, C3H, C6H), 2.84 (m, 1H, C4H), 1.54 (m, 2H, $C5H_2$), 1.42 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.1 (C=O ester), 155.1 (NC=O), 135.4, 128.4, 127.7 (Arom.), 135.0, 130.2 (C7, C8), 80.8 ($\underline{C}(CH_3)_3$), 66.8 ($PhCH_2O$), 47.4 (C1), 47.1 (C3), 44.8 (C6), 30.6 (C4), 28.0

($C(\underline{C}H_3)_3$), 25.8 (C5). MS (DIC, NH_3) : *m/e* 344 $[M+H]^+$, 361 $[M+NH_4]^+$. Anal. Calcd. for $C_{20}H_{24}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found : C, 69.80; H, 7.45; N, 3.89.

Compound **9c** : This compound was prepared according reference 12.^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5H, Arom), 6.42 and 6.32 (2m, 2H, C8H and C7H), 5.27 (m, 3H, $CO_2C\underline{H}_2Ph$ and C1H), 3.62 (s, 3H, CO_2CH_3), 3.25 (m, 1H, C3H), 3.03 (m, 2H, C3H and C6H), 2.81 (m, 1H, C4H), 1.87 (m, 2H, C5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.1 (CO ester), 155.2 (NC=O), 135.5 and 130.6 (C8 and C7), 136.8, 128.5, 127.8, 126.9 (C Arom), 66.9 ($CO_2\underline{C}H_2Ph$), 51.9 ($CO_2\underline{C}H_3$), 47.4 (C3), 46.7 (C1), 43.9 (C6), 30.6 (C4), 26.0 (C5). MS (DIC, NH_3) : m/e 302 $[M+H]^+$, 319 $[M+NH_4]^+$.

Preparation of cyclohexadiene derivative **10a**. To a solution of isoquinuclidine **9a** (721 mg, 2.7 mmol) in THF (20 ml) was added at - 40° C a solution of LiHMDS in THF (1M, 5.4 ml, 2 equiv) . The reaction medium was stirred 2 hours and cooled again at - 40° C. A solution of LiHMDS in hexane (1M, 2.7 ml, 1 equiv) was added. After 30 mn at - 40° C, an excess of methyl iodide (10 ml) was added.The reaction was stirred 12 hours at room temperature, hydrolyzed with a solution of ammonium chloride and extracted with dichloromethane. A column chromatography (AcOEt/Pentane: 30:70) afforded compound **10a** (679 mg, 89%).

Compound **10a** : $[\alpha]_D^{20}$ +223.5 (c 0.885, $CHCl_3$) ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.92 (d, 1 H, C2H, J = 6 Hz), 6.11 (dd, 1 H, C3H), 5.99 (m; 1H, C4H), 3.68 (s, 3H, CO_2CH_3), 3.40 to 3.10 (m, 2H, $C5C\underline{H}_2N$), 2.90 (2s, 3H, NCH_3), 2.70 (m, 1H, C6H), 2.67 (m, 1H, C5H), 2.29 (m, 1H, C6H), 1.5 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166 (CO ester), 156.6 (NC=O), 133.7 (C2), 131.4 (C4), 127.9 (C1), 124.4 (C3), 79.7 ($\underline{C}(CH_3)_3$), 52 ($NCO_2\underline{C}H_3$), 50.6 ($C5\underline{C}H_2N$), 34.8 (C5), 32.0 (NCH_3), 27.5 ($C(\underline{C}H_3)_3$), 24.0 (C6). MS (DIC, NH_3) : m/e 282 $[M+H]^+$, 299 $[M+NH_4]^+$.

Preparation of cyclohexadiene derivative **10b.** Experimental condition, see : preparation of compound **10a**. Compound **9b** (2.3g, 6.7 mmol) afforded compound **10b** (1.45g, 61%) after column chromatography (Heptane/AcOEt: 70:30)

Compound **10b** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38 (m, 5H, Arom.), 6.91 (m, 1H, C2H), 6.02 (m, 2H, C3H and C4H), 5.12, (m, 2H, $CO_2C\underline{H}_2Ph$), 3.37 (m, 1H, $C5C\underline{H}$-N), 3.15 (m, 1H, $C5C\underline{H}$-N), 2.94 (s, 3H, NCH_3), 2.74 (m, 1H, C5H), 2.48 (dd, 1H, C6H, J = 16, 10 Hz), 2.27 (dd, 1H, C6H, J = 16, 7 Hz), 1.5 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.1 (CO ester), 156 (NC=O), 136.6 (C Arom.), 133.9 (C1) 131.4 (C2), 128.2 127.5 and 124.4 (C Arom., C3 and C4), 79.3 ($\underline{C}(CH_3)_3$), 66.7 ($CO_2\underline{C}H_2Ph$), 51.2 ($C5\underline{C}H_2N$), 35 (C5), 32.3 (NCH_3), 27.8 ($C(\underline{C}H_3)_3$), 24.4 (C6). MS (DIC, NH_3) : m/e 358 $[M+H]^+$, 375 $[M+NH_4]^+$.

Preparation of diols **11** and **12**. To a solution of ADmixβ (154 mg, 1.4 g/1 mmol of substract) and methane sulfonamide (15 mg, 1.5 equiv) in a mixture tBuOH/H_2O: 1:1 (2ml) was added at 20° C a solution of cyclohexadiene derivative **10a** (30mg, 0.11 mmol). The resulting mixture was stirred at 20° C for 20 hours. Sodium sulfite (160 mg, 7 equiv) was added and the mixture was stirred for additionnal 30 mn. After extraction with ethyl acetate, the organic phase was successively washed with water and brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. After purification by preparative TLC (CH_2Cl_2/MeOH: 96:4) compounds **12** (6 mg, 18%) and **11** (10 mg, 29%) were isolated.

Compound **11** : $[\alpha]_D^{20}$ -81 (c 0.63, $CHCl_3$) ^1H NMR (250 MHz, $CDCl_3$) δ 6.85 (bd, 1H, C2H), 4.39 (m, 1H, C3H), 4.29 (m, 1H, C4H), 4.02 (m, 1H, C5C<u>H</u>N), 3.68 (NCO_2CH_3), 3.50 (m, 1H, C5C<u>H</u>N), 2.98 (s, 3H, NCH_3), 2.55 (m, 1H, C6H), 2.03 (m, 2H, C6H and C5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166 (CO ester), 158.3 (NC=O), 135.1 (C2), 134.0 (C1), 80.7 ($\underline{C}(CH_3)_3$), 70.5 and 65.7 (C3 and C4), 53.1 ($CO_2\underline{C}H_3$), 51.1 ($C5\underline{C}H_2N$), 42.7 (C5), 36.9 ($N\underline{C}H_3$), 35.1 (C6), 28.5 ($C(\underline{C}H_3)_3$). MS (DIC, NH_3) : m/e 316 $[M+H]^+$, 333 $[M+NH_4]^+$

Compound **12** : $[\alpha]_D^{20}$ -22.3 (c 0.66, $CHCl_3$) ^1H NMR (250 MHz, $CDCl_3$) δ 6.65 (bs, 1H, C2H), 4.24(m, 1H, C3H), 3.87 (dd, 1H, C5CHN, J = 4.5, 14 Hz), 3.80 (m, 1H, C4H), 3.70 (s, 3H, NCO_2CH_3), 2.89 (s, 3H, NCH_3), 2.76 (m, 1H, C5CHN, J = 10.5, 14 Hz), 2.18 (m, 1H, C6H), 2.02 (m, 1H, C5H), 1.90 (m, 1H, C6H), 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.9 (CO ester), 158.6 (NC=O), 138.2 (C2), 131.1 (C1), 80.6 ($\underline{C}(CH_3)_3$), 68.5 and 65.7 (C3 and C4), 52.7 ($CO_2\underline{C}H_3$), 50.8 ($C5\underline{C}H_2N$), 35.9 (C5), 34.8 ($N\underline{C}H_3$), 28.1 ($C(\underline{C}H_3)_3$), 23.6 (C6). MS (DIC, NH_3) : m/e 316 $[M+H]^+$, 333 $[M+NH_4]^+$.

Preparation of the bicyclic oxazinone derivative **13**. To a solution of diol **11** (44 mg, 0.14 mmol) in THF (2ml) was added at room temperature a solution of LiHMDS in THF (1M, 0.3 ml, 2 equiv). The reaction medium was stirred 18 hours at 40° c, hydrolised with a solution of ammonium chloride and extracted with ethyl acetate. After purification by preparative TLC (CH_2Cl_2/MeOH: 96:4) compound **13** (18 mg, 45%) was isolated.

Compound **13 :** $[\alpha]_D^{20}$ -71 (c 0.465, $CHCl_3$) ^1H NMR (200 MHz, $CDCl_3$) δ 6.88 (dd, 1H, C2H, J = 5.5, 2 Hz), 4.47 (dd, 1H, C3H, J = 5.5, 3.5 Hz), 4.08 (dd, 1H, C4H, J = 3.5, 12 Hz), 3.39 (dd, 1H, C5CHN, J = 12, 6 Hz), 3.19 (dd, 1H, C5CHN, J = 12, 12 Hz), 3.03 (s, 3H, NCH_3), 2.80 (dd, 1H, C6H, J = 18, 5.5 Hz), 2.52 (m, 1H, C5H, J = 12, 6, 6, 12, 12 Hz), 1.93 (ddd, 1H, C6H, J = 18, 2, 12 Hz), 1.5 (s, 9H, $C(CH_3)_3$). MS (DIC, NH_3) : m/e 284 $[M+H]^+$, 301 $[M+NH_4]^+$.

Preparation of compound **14.** To a solution of the bicyclic derivative oxazinone derivative **13** (20 mg, 0.07 mmol) in dry DMF (1 ml) at - 40° C was added a solution of LiHMDS in THF (0.1 ml, 1.5 equiv). After 20 min at this temperature, a solution of propargyl bromide in toluene (0.012 ml, 1.5 equiv) was added dropwise. The reaction medium was stirred at - 40° C for additional 1 hour and allowed to rise to room temperature, hydrolised with a solution of ammonium chloride and extracted with ethyl acetate. A purification by preparative TLC (CH_2Cl_2/MeOH: 95:5) afforded compound **14** (15 mg, 66%).

Compound **14** : $[\alpha]_D^{20}$ -124 (c 0.91, $CHCl_3$) ^1H NMR (250 MHz, $CDCl_3$) δ 6.86 (dd, 1H, C2H, J = 5, 2.5 Hz), 4.47 (d, 2H, $CHCC\underline{H}_2O$, J = 2.5 Hz), 4.33 (dd, 1H, C3H, J = 5, 3.5 Hz), 4.16 (dd, 1H, C4H, J = 3.5, 12 Hz), 3.88 (dd, 1H, C5CHN, J = 11.5, 6 Hz), 3.18 (dd, 1H, C5CHN, J = 11.5, 12 Hz), 3.02 (s, 3H, NCH_3), 2.78 (dd, 1H, C6H, J = 18, 6 Hz), 2.56 (m, 1H, C5H, J = 6, 12, 6, 12, 12 Hz), 2.49 (t, 1H, $C\underline{H}CCH_2O$, J = 2.5 Hz), 1.89 (ddd, 1H, C6H, J = 18, 12, 2 Hz), 1.49 (s, 9H, $C(CH_3)_3$). MS (DIC, NH_3) : m/e 322 $[M+H]^+$, 339 $[M+NH_4]^+$.

Preparation of oxahydrindane derivative **15**. A solution of compound **14** (16 mg, 0.05 mmol), tributyltin hydride (0.027, 2 equiv) and trace amount of AIBN in toluene (4 mL) was refluxed for 5 hours. The reaction mixture was evaporated *in vacuo* and filtered on a silica column (Pentane then CH_2Cl_2 : MeOH :

90 : 10). An additionnal purification by preparative TLC (Pentane/AcOEt: 50:50) afforded a mixture of diastereoisomers **15** (16 mg, 52%).

Compound **15** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.91, 5.87 (2x2d, 1H, C9H, J = 1.5, 52 Hz), 4.52-4.31 (m, 1H, C6H), 4.29-3.99 (m, 3H, C5H, C8aH_2), 3.32 (m, 3H, C4CHN), 3.22 (m, 1H, C2H), 2.99 (m, 3H, NCH_3), 2.79-2.30 (m, 3H, C4CHN, C4H, C7H), 2.18-1.88 (m, 2H, C3H_2), 1.61-1.41 (m, 24H, C($C\underline{H}_3$)$_3$, $SnBu_3$), 1.01-0.79 (m, 12H, $SnBu_3$). MS (DIC, NH_3) : *m/e* 615 $[M+H]^+$, 632 $[M+NH_4]^+$.

Preparation of epoxide **16b**. To a solution of cyclohexadiene derivative **10b** (3.4 g, 9.5 mmol) in dichloromethane (80 ml) was added by small fractions *m*-CPBA (12 g, 1.2 equiv). The reaction medium was stirred 3 hours at room temperature, hydrolised with an aqueous solution of sodium carbonate (10%) and extracted with dichlomethane. Usual work up afforded quantitatively epoxide **16b** (3.55g, 100%).

Compound **16b** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5H, Arom), 6.96 (m, 1H, C2H), 5.12 (m, 2H, $CO_2C\underline{H}_2$Ph), 3.41 (m, 3H, C3H, C4H and C5CHN), 3.02 (s, 3H, NCH_3), 2.92 (m, 1H, C5CHN), 2.47 (m, 1H, C5H), 2.16 (m, 1H, C6H), 1.70 (m, 1H, C6H), 1.45 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.1 (CO ester), 156.4 (NC=O), 136.7 (C1), 132.1 (C2), 135.5, 128.5, 128.0, 127.9 (C Arom), 81 ($\underline{C}(CH_3)_3$), 67.2 ($CO_2\underline{C}H_2Ph$), 57 (C3), 52.6 (C5$\underline{C}H_2N$), 47.7 (C4), 36.1 (NCH_3), 32.8 (C5), 28 (C($\underline{C}H_3$)$_3$), 23.4 (C6). MS (DIC, NH_3) : m/e 374 $[M+H]^+$, 391 $[M+NH_4]^+$.

Preparation of epoxide **16c**. The same experimental conditions permitted to prepare quantitatively epoxide **16c** from cyclohexadiene derivative **10c**.

Compound **16c** : ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32 (bs, 5H, Arom), 7.04 (m, 1H, C2H), 5.12 (m, 2H, $CO_2C\underline{H}_2$PH), 3.72 (s, 3H, OCH_3), 3.61 to 3.29 (m, 3H, C5H, C4H and C5CHN), 3.02 (s, 3H, NCH_3), 2.92 (bs, 1H, C5CHN), 2.52 (m,1H, C5H), 2.21 (m, 1H, C6H), 1.82 (m, 1H, C6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.1 (CO ester), 156.2 (NC=O), 136.5 (C1), 131.5 (C2), 133.5, 128.4, 127.8 and 127.7 (C Arom), 67.0 ($CO_2\underline{C}H_2$Ph), 56.9 (C3), 51.9 ($O\underline{C}H_3$), 48.7 (C5$\underline{C}H_2N$), 47.3 (C4), 35.2 (NCH_3), 32.5 (C5), 23.6 (C6). MS (DIC, NH_3) : m/e 332 $[M+H]^+$, 349 $[M+NH_4]^+$.

Preparation of acetate derivative **17**. To a slurry of neutral activated alumina (10 g) in ether was added an excess of acetic acid (2 ml). After 20 mn at room temperature, a solution of epoxide **16c** (1 g, 3 mmol) in the minimum of ether was added. The resulting mixture was stirred 3 days at room temperature. After filtration on celit, the solution was neutralised with an aqueous solution of sodium carbonate (10%) and extracted with dichlomethane. Purification by column chromatography (AcOEt/Heptane: 50:50) afforded epoxide **16c** (69 mg), acetate derivative **17** (520 mg, 44%) and the regioisomer (66 mg, 6%).

Compound **17** : ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 (bs, 5H, Arom), 6.84 (bd, 1H, C2H, J = 4.5 Hz) 5.22 (m, 1H, C3H), 5.13 (2d, 2H, $CO_2C\underline{H}_2$Ph, J = 14.5Hz), 3.96 (d, 1H, OH, J = 4.5 Hz), 3.82 (dd, 1H, C5HN, J = 14, 10.5 Hz), 3.72 (s, 3H, OCH_3), 3.63 (m, 1H, C4H), 2.95 (s, 3H, NCH_3), 2.88 (dd, 1H, C5HN, J = 14, 3.5 Hz), 2.3 (m, 2H, C6H and C5H), 2.12 (bd, 1H, C6H) 2.02 (s, 3H, CH_3CO). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.3 ($CH_3\underline{C}O$), 166.5 (CO ester), 157.6 (NC=O), 136 (C Arom) 133.8 (C1), 131.3 (C2), 128.3, 127.9 and 127.6 (C Arom), 69 (C3), 67.5 ($\underline{C}H_2$Ph), 65.5 (C4), 51.8 (OCH_3), 49.3 (C5$\underline{C}H_2N$), 34.7 (NCH_3), 32.4 (C5), 23.5 (C6), 21.0 ($\underline{C}H_3CO$). MS (DIC, NH_3) : m/e 392 $[M+H]^+$, 409 $[M+NH_4]^+$.

Preparation of compound **18**. A solution of epoxide **16b** (1 g, 2.7mmol), cerium ammonium nitrate (294 mg, 0.2 equiv) and propargyl alcohol (1.6 ml, 10 equiv) in dichlomethane (20 ml) was stirred 20 hours at room temperature. The organic phase was washed with water. Usual work up and purification by column chromatography (Pentane/AcOEt: 20:80) afforded nitro compound (71 mg, 6%), epoxide **16b** (63 mg) and compound **18** (520 mg, 45%).

Compound **18** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38 (bs, 5H, Arom), 6.85 (bd, 1H, C2H, J = 4.5 Hz), 5.18 (bs, 2H, $CO_2C\underline{H_2}Ph$), 4.22 (d, 2H, $CHCC\underline{H_2}O$, J = 2.5 Hz), 4.13 (m, 1H, C3H), 3.98 (bd, 1H, OH, J = 4.5 Hz), 3.87 (dd, 1H, C5CHN, J = 14, 11 Hz), 3.77 (m, 1H, C4H), 2.97 (s, 3H, NCH_3), 2.86 (d, 1H, C5CHN, J = 14, 4 hz), 2.42 (t, 1H, $C\underline{H}CCH_2O$), J = 2.5 Hz), 2.22 (m, 1H, C6H), 2.01 (m, 2H, C5H and C6H), 1.48 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.6 (CO ester), 158.2 (NC=O), 136.4, 128.5, 128.2, 127.9 (C Arom), 134.6 (C1), 131.6 (C2), 80.6 ($\underline{C}(CH_3)_3$), 79.6 ($\underline{C}HCCH_2O$), 74.7 ($CH\underline{C}CH_2O$), 74.5 (C3), 67.6 ($CO_2\underline{C}H_2Ph$), 65.0 (C4), 57 ($CHC\underline{C}H_2O$), 50.2 ($C5\underline{C}H_2N$), 34.6 (NCH_3), 32 (C5), 28.0 ($C(\underline{C}H_3)_3$), 23.6 (C6). MS (DIC, NH_3) : m/e 430 $[M+H]^+$, 447 $[M+NH_4]^+$.

Preparation of compounds **19**. To a stirred solution of *para*-methoxythiophenol (0.067 ml, 5equiv) in THF (1 ml) was added at 0° C a solution of LiHMDS in THF (1M, 0.44 ml, 4 equiv).After 20 mn a solution of compound **17** (43 mg, 0.11 mmol), in THF (0.5 ml) was added at 0° C to the THF solution of thiophenate.The reaction medium was allowed to rise to room temperature.After 3 hours, the reaction mixture was evaporated *in vacuo* , extracted with dichlomethane and washed successively with water and brine. A purification by preparative TLC (AcOEt/Heptane: 60:40) afforded two diastereoisomers **19** (10 and 26 mg, 17%, 45%).

Major compound **19** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 (bs, 5H, $CO_2CH_2\underline{Ph}$), 7.26 (d, 2H, $CH_3O\underline{Ph}S$, J = 8.9 Hz), 6.78 (d, 2H, $CH_3O\underline{Ph}S$, J = 8.9 Hz), 5.12 (m, 2H, $CO_2C\underline{H_2}Ph$), 4.72 (bs, 1H, C4H), 4.48 (bs, 1H, C3H), 3.72 (s, 3H, $C\underline{H_3}OPhS$), 3.59 (bs, 1H, C2H), 3.52 to 3.38 (m, 1H, C5CHN), 3.33 (s, 3H, $CO_2C\underline{H_3}$), 3.13 (m, 2H, C5CHN and C1H), 2.89 (s, 3H. NCH_3), 2.32 (m, 1H, C5H), 2.11 (s, 3H, CH_3CO), 1.91 (m, 1H, C6H), 1.69 (m, 1H, C6H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.3 ($CH_3\underline{C}O$), 171.1 (CO ester), 156.3 (NC=O), 159.0, 136.5, 134.2, 128.3, 127.8, 127.6, 127.2, 114.5 and 114.2 (C Arom), 70.8 (C3), 69.3 (C4), 67.2 ($CO_2\underline{C}H_2Ph$) 55.1 ($\underline{C}H_3OPhS$), 53.3 ($CO_2\underline{C}H_3$), 51.0 (C2), 50.3 ($C5\underline{C}H_2N$), 41.2 (C1), 35.2 (NCH_3), 32.8 (C5), 21.8 (C6), 21.1 ($\underline{C}H_3CO$). MS (DIC, NH_3) : m/e 532 $[M+H]^+$, 549 $[M+NH_4]^+$.

Minor compound **19** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39 (d, 2H, $CH_3O\underline{Ph}S$, J = 8.9 Hz), 7.33 (bs, 5H, $CO_2CH_2\underline{Ph}$), 6.82 (d, 2H, $CH_3O\underline{Ph}S$, J = 8.9 Hz), 5.28 (m, 1H, C3H, J = 4.3, 1 Hz)), 5.08 (dd, 2H, $CO_2C\underline{H_2}Ph$, J = 11.8 Hz), 4.22 (d, 1H, OH, J = 4.3 Hz), 3.77 (m and s, $C\underline{H_3}OPhS$ and C5CHN), 3.68 (s, 3H, CO_2CH_3), 3.59 (bs, 1H, C4H), 3.48 (dd, 1H, C2H, J = 12.3 Hz), 2.88 (s, 3H, NCH_3), 2.78 (m, 1H, C1H), 2.51 (dd, 1H, C5CHN), 2.07 (s, 3H, $C\underline{H_3}CO$), 2.02 (m, 1H, C5H), 1.78 (m, 1H, C6H), 1.56 (m, 1H, C6H). ^{13}C NMR (5O MHz, $CDCl_3$) δ 174.1 ($CH_3\underline{C}O$), 169.6 (CO ester), 157.5 (NC=O), 159.6, 156.2, 135.4, 135.0, 134.2, 127.9, 127.6, 124.2, 123.2, 114.7, 114.5 (C Arom), 72.0 (C3), 67.5 ($CO_2\underline{C}H_2Ph$), 66.0 (C4), 55 ($\underline{C}H_3OPhS$), 51.6 ($CO_2\underline{C}H_3$), 50.9 ($C5\underline{C}H_2N$), 49.5 (C2), 44.5

(C1), 35.1 (NCH_3), 33.2 (C5), 28.2 (C6), 20.8 ($\underline{C}H_3CO$). MS (DIC, NH_3) : m/e 532 $[M+H]^+$, 549 $[M+NH_4]^+$.

Preparation of compounds **20**. Before Michael's reaction, compound **18** was transformed quantitavely to methyl ester with a solution of methanol saturated with HCl gas. To a stirred solution of *para*-methoxythiophenol (O.093 ml, 4 equiv) in THF(0.5 ml) was added a solution of LiHMDS in THF (1M, 0.56 ml, 3 equiv) at room temperature. A solution of methyl ester (73 mg, 0.19 mmol) in THF (1 mL) was added to the THF solution of thiophenate. After 5 hours, the reaction mixture was evaporated *in vacuo*, extracted with dichloromethane and washed successively with water and brine. After purification by preparative TLC (Pentane/AcOEt: 70:30), a mixture of diastereoisomers **20** was isolated (69 mg, 69%).

Compound **20** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (m, 2H, $CH_3O\underline{Ph}S$), 7.25 (brs, 5H, $CO_2CH_2\underline{Ph}$), 6.72 (m, 2H, $CH_3O\underline{Ph}S$), 5.02 (m, 2H, $CO_2C\underline{H_2}Ph$), 4.39-3.89 (m, 4H, C3H, C4H, $HCCC\underline{H_2}O$), 3.65 (2s, 6H, CH_3OPhS, CO_2CH_3), 3.08 (m, 1H, C2H), 2.92 (m, 3H, NCH_3), 2.87 (m, 1H, C5CHN), 2.58 (m, 1H, C1H), 2.40 (brs, 1H, $\underline{H}CCCH_2O$), 2.23 (m, 1H, C5CHN), 2.10-1.90 (m, 3H, C5H, $C6H_2$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.1 (C=O ester), 157.9 (NC=O), 159.3, 134.9, 125.8, 114.5 ($CH_3O\underline{Ph}S$), 135.5, 128.5, 128.2, 127.9 (CO_2CH_2Ph), 80.1 ($H\underline{C}CCH_2O$), 78.7 (C3), 74.8 ($HC\underline{C}CH_2O$), 67.5 ($CO_2\underline{C}H_2Ph$), 65.4 (C4), 58.5 ($HCC\underline{C}H_2O$), 55.3 ($\underline{C}H_3OPhS$), 51.6 ($CO_2\underline{C}H_3$), 50.8 (C2), 50.2 ($C5\underline{C}H_2N$), 41.9 (C1), 35.2 (NCH_3), 32.8 (C5), 21.1 (C6). MS (DIC, NH_3) : *m/e* 528.$[M+H]^+$, 545 $[M+NH_4]^+$.

Preparation of chloro thioether **21**. To a solution of major diastereoisomer **19** (47 mg, 0.09mmol) in dichloromethane (4 ml) was added dropwise at 0° C a solution of sulfuryl chlorid (0.05 ml, 7 equi) in dichloromethane (2 ml).The reaction medium was stirred for additional 20 mn at 0° C and evaporated *in vacuo*. A purification by preparative TLC (AcOEt/Heptane: 50:50) afforded **21** (24 mg, 48%).

Compound **21** : ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (bs, 7H, $CO_2CH_2\underline{Ph}$ (5H) and $CH_3O\underline{Ph}S$ (2H)), 6.88 (d, 2H, $CH_3O\underline{Ph}S$, J = 6.2 Hz), 5.12 (m, 3H, $CO_2C\underline{H_2}Ph$ and C3H), 4.28 (bs, 1H, C4H), 3.78 (, 3H, $C\underline{H_3}OPhS$), 3.61 (s, 3H, $CO_2C\underline{H_3}$), 3.58 (m, 1H, C5CHN), 3.42 to 3.19 (m, 2H, C5CHN and C1H), 2.92 (s, 3H, NCH_3), 2.90 to 2.66 (m, 1H, C6H), 2.18 (s, 3H, CH_3CO), 2.17 to 2.08 (m, 1H, C5H), 1.68 (m, 1H, C6H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.7 ($CH_3\underline{C}O$), 167.7 (CO ester), 156.5 (NC=O), 161.6, 139.8 139.5, 136.7, 132.4, 128.5, 128.0, 127.9, 120.0, 114.8, 114.6 and 114.3 (C Arom), 82.3 (C2), 75.2 (C3), 71.5 (C4), 67.3 ($N\underline{C}H_2Ph$), 55.5 ($\underline{C}H_3OPhS$), 53.2 ($CO_2\underline{C}H_3$), 49.2 ($C5\underline{C}H_2N$), 35.4 (C5), 34.0 (C6), 29.4 (NCH_3), 28.7 (C1), 21.6 ($\underline{C}H_3CO$). MS (DIC, NH_3) : m/e 567 $[M+H]^+$.

Preparation of iodo derivative **22**. To a solution of compound **10b** (101 mg, 0.28 mmol) in dichloromethane (2 ml) was added a solution of I_2 (108 mg, 1.5 equiv) in dichloromethane. The reaction medium was stirred 6 hours at room temperature. The organic phase was washed with an aqueous solution of $Na_2S_2O_3$ (10%).After usual work up and purification by preparative TLC (AcOEt/Pentane: 50:50) iodo derivative **22** was isolated (72 mg, 65%).

Compound **22** : ^1H NMR (250 MHz, $CDCl_3$) δ 6.92 (m, 1H, C2H), 4.98 (m, 1H, C3H, J = 4.5 Hz), 4.78 (s, 1H, C4H), 3.70 (dd, 1H, $C5C\underline{H}N$, J = 12.5, 5 Hz), 3.11 (d, 1H, $C5C\underline{H}N$, J = 12.5 Hz), 3.01 (s, 3H, NCH_3), 2.85 (m, 1H, C5H), 2.72 (dd, 1H, C6H, J = 17.5, 6 Hz), 2.52 (bddt, 1H, C6H, J =

17.5, 10.5, 2.5, 2.5 Hz), 1.48 (s, 9H, $C(C\underline{H}_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.8 (CO ester), 152.1 (C=O), 134.6 (C2), 130.0 (C1), 81.4 ($\underline{C}(CH_3)_3$), 51.9 ($C5\underline{C}H_2N$), 36.5 (C5), 28.1 ($C(\underline{C}H_3)_3$), 24.9 (C3), 22.9 (C6), 20.9 (NCH_3). MS (DIC, NH_3) : m/e 394 $[M+H]^+$, 411 $[M+NH_4]^+$.

Preparation of compounds **23** and **24.** General procedure. To a solution of cyclohexadiene derivative **10b** in alcohol (methyl or benzyl) was added mercuric acetate (2 equiv). The reaction medium was stirred 24 hours at room temperature. The excess of alcohol was distillated *in vacuo* and an aqueous saturated KCl solution was added. The solution was stirred 3 hours at room temperature and then extracted with CH_2Cl_2. After purification by preparative TLC (CH2Cl2/MeOH: 98:2) compound **10b** (55 mg, 0.15 mmol) afforded **23** (70 mg, 73%) and the regioisomer (13%). Cyclohexadiene derivative **10b** (198 mg) afforded without purification compound **24** (301 mg, 77%).

Compound **23** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.39 (m, 5H, Arom), 6.94 (d, 1H, C2H, J = 5.3 Hz), 5.18 (m, 2H, $CO_2C\underline{H}_2Ph$), 4.08 (d, 1H, C3H, J = 5.3 Hz), 3.67 (m, 1H, C5C$\underline{H}$N), 3.36 (s, 3H, OCH_3), 3.03 (m, 2H, C5C$\underline{H}$N and C4H), 2.97 (s, 3H, NCH_3), 2.68 (m, 1H, C5H), 2.51 (dd, 1H, C6H), 1.68 (m, 1H, C6H), 1.49 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.6 (CO ester), 157.7 (NC=O), 136.6, 128.6, 128.2 (C Arom), 134.7 (C1), 134.3 (C2), 81.0 ($\underline{C}(CH_3)_3$), 75.0 (C3), 67.6 ($CO_2\underline{C}H_2Ph$), 57.0 (OCH_3), 54.9 (C4), 54.0 ($C5\underline{C}H_2N$), 34.3 (C5), 32.6 (NCH_3), 31.6 (C6), 28.0 ($C(CH_3)_3$).

Compound **24** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (m, 10H, Arom), 6.91 (bd, 1H, C2H), 5.16 (m, 4H, $CO_2C\underline{H}_2Ph$ and $PhC\underline{H}_2O$), 4.31 (d, 1H, C3H, J = 5.9 Hz), 3.68 (m, 1H, C5CHN), 3.01 (m, 2H, C5CHN and C4H), 2.93 (m, 1H, C5H), 2.49 (dd, 1H, C6H), 1.60 (m, 1H, C6H), 1.49 (s, 9H, $C(CH_3)_3$).

Preparation of compounds **25**, **26** and **27**. To a solution of $NaBH_4$ (8 mg) in DMF (2 ml) saturated in O_2 was added dropwise under O_2 atmosphere a solution of compound 24 (71 mg, 0.11 mmol) in DMF (3 ml). The reaction medium was stirred 4 hours at room temperature, filtered, treated with an aqueous solution of sodium carbonate (10%) and extracted with ethyl acetate. A purification by preparative TLC (AcOEt/Pentane: 30:70) afforded the two alcohols **25** and **26** (15 mg, 9 mg, 33%, 20%).When the solution was not over saturated with O_2 compound **27** was also isolated.

Compound **25** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.38 (bs, 5H, Arom), 6.48 (bd, 1H, C2H), 5.18 (s, 2H, $CO_2C\underline{H}_2Ph$), 3.87 (m, 1H, C5C$\underline{H}$N), 3.79 m, 1H, C3H), 3.19 (bs, 1H, C4H), 3.42 (s, 3H, OCH_3), 2.97 (s, 3H, NCH_3), 2.87 (dd, 1H, C5CHN, J = 14.8, 11.9 Hz), 2.22 (m, 1H, C6H), 1.99 (m, 2H, C5H and C6H), 1.48 (s, 9H, $C(C\underline{H}_3)_3$). MS (DIC, NH_3) : m/e 406 $[M+H]^+$, 423 $[M+NH_4]^+$.

Compound **26** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.33 (bs, 5H, Arom), 6.86 (d, 1H, C2H), 5.12 (bs, 2H, $CO_2C\underline{H}_2Ph$), 3.96 (m, 1H, C3H), 3.72 to 3.48 (s and m, 5H, OCH_3, C4H and C5C$\underline{H}$N), 2.97 (s, 3H, NCH_3), 2.58 (dd, 1H, C5C$\underline{H}$N), 2.22 (m, 1H, C6H), 1.99 (m, 1H, C5H), 1.68 (m, 1H, C6H), 1.47 (s, 9H, $C(C\underline{H}_3)_3$). MS (DIC, NH_3) : m/e 406 $[M+H]^+$, 423 $[M+NH_4]^+$.

Compound **27** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.33 (bs, 5H, Arom), 6.39 (bs, 1H, C2H), 5.12 (bs, 2H, $CO_2C\underline{H}_2Ph$), 3.87 (bd, 1H, C3H), 3.38 (s, 3H, OCH_3), 3.28 (m, 2H, $C5C\underline{H}_2N$), 2.98 (s, 3H, NCH_3), 2.49 (dd, 1H, C4H), 2.11 (m, 1H, C5H), 1.87 (m, 2H, C4H and C6H), 1.48 (s, 9H, $C(CH_3)_3$), 1.28 (m, 1H, C6H). MS (DIC, NH_3) : m/e 390 $[M+H]^+$, 407 $[M+NH_4]^+$.

Preparation of diol **28**. To a solution of isoquinuclidine **9b** (1.716 g, 5 mmol) in acetone (40mL) at 20°C was added successively osmium tetroxide in solution in *ter*-butanol (2.5%, 1.3 mL, 0.02 equiv.), *N*-methylmorpholine *N*-oxide (8.62 mg, 1.5 equiv.), methanesulfonamide (712 mg, 1.5 equiv.). The resulting mixture was stirred at 20°C for 4 hours. An aqueous solution of sodium sulfite (10%, 20mL) was then added and the reaction mixture was stirred for additional 30 minutes. After extraction with dichloromethane, the organic phase was successively washed with a saturated solution of ammonium chloride and brine, dried over magnesium sufate, filtrated and concentrated *in vacuo*. The crude product ((1.735 g, 92%) was used in the following step without further purification.

Compound **28** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (br. s, 5H, Arom.), 5.11 (m, 2H, $PhCH_2O$), 4.39 (br. s, 1H, C1H), 3.86 (m, 2H, C7H, C8H), 3.69 (m, 1H, C3H), 3.12 (m, 1H, C3H), 2.85 (m, 1H, C6H), 1.97 (m, 2H, C4H, C5H), 1.75 (m, 1H, C5H), 1.41 (s, 9H, 3 $C(CH_3)_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.7 (C=O ester), 156.7 (NC=O), 136.4, 128.4, 127.9, 127.6 (arom.), 81.5 ($\underline{C}(CH_3)_3$), 67.1 ($PhCH_2O$), 65.5, 65.0 (C7, C8), 51.5 (C1), 41.9 (C6), 41.3 (C3), 32.7 (C4), 27.9 ($C(\underline{C}H_3)_3$), 23.7 (C5). MS (DIC, NH_3) : *m/e* 378 $[M+H]^+$, 395 $[M+NH_4]^+$.

Protection of diol **28**. A solution of diol **28** (1.426 g, 4.73 mmol) and *para*-toluenesulfonic acid (90 mg, 0.1 equiv) in 2,2-dimethoxypropane (10mL) was stirred at room temperature for 12 hours. The reaction medium was concentrated *in vacuo* to 5mL and extracted with dichloromethane. The organic phase was washed successively with an aqueous solution of sodium carbonate and brine. After usual work up, diol **28** acetonide was obtained quantitatively (1.615 g, 4.73 mmol).

Preparation of compound **29.** A solution of diol **28** acetonide (937 mg, 2.24 mmol) in methanol (10mL) was stirred for 2 hours under hydrogen atmosphere in the presence of Pd-C (10%w/w). An excess of aqueous solution of formaldehyde was then added and the reaction mixture was stirred under hydrogen for additional 2 hours. Filtration on celite, followed by evaporation *in vacuo* afforded a crude product which was purified by chromatography on silica gel (AcOEt/MeOH: 85:15) affording **29** (571 mg, 90%).

Compound **29** : $[\alpha]_D^{20}$ -53 (c 1.25, $CHCl_3$). IR ($CHCl_3$) : 2980, 2920, 1730. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.13 (1H, dd, C8H, J = 3.5, 6.5 Hz), 4.05 (1H, dd, C7H, J = 2, 6.5 Hz), 3.12 (2H, m, C1H, C3H, J = 2, 3, 10 Hz), 2.97 (1H, ddd, C6H, J = 3, 5, 11 Hz), 2.48 (3H, s, CH_3N) 2.34 (1H, m, C3H, J = 10 Hz), 2.00 (1H, m, C4H, J = 3, 3.5, 4 Hz), 1.92 (1H, dm, C5H, J = 5, 14 Hz, 1.74 (1H, ddd, C5H, J = 4, 11, 14 Hz), 1.56 (3H, s, $C(CH_3)_2$), 1.44 (9H, s, $C(CH_3)_3$), 1.32 (3H, s, $C(CH_3)_2$).^{13}C NMR (50 MHz, $CDCl_3$) δ 173.2 (C=O ester), 108.7 ($\underline{C}(CH_3)_2$), 80.7 ($\underline{C}(CH_3)_3$), 74.8, 73.7 (C7 et C8), 56.8 (C1), 49.0 (C3), 43.8 (CH_3N), 38.9 (C6), 30.8 (C4), 28.0 ($C(\underline{C}H_3)_3$), 25.9, 24.4 ($C(\underline{C}H_3)_2$), 23.0 (C5). MS (DIC, NH_3) : *m/e* 298 $[M+H]^+$.

Preparation of compounds **30a** or **30b**. A solution of compound **29** (1g, 3.37mmol) in methyl iodide (5mL) or benzyl bromide (5mL) was stirred at room temperature for 4 hours. Evaporation of excess of methyl iodide afforded quantitatively compound **29** methiodide. The reaction mixture containing an excess of benzyl bromide was diluted with a mixture of diethylether-pentane (50:50) affording a white precipitate which was filtered off and dried *in vacuo*. The resulting ammonium salts in suspension in THF (30mL) was stirred in the presence of potassium *ter*-butoxide (450 mg, 4.01 mmol, 1.2 equiv) at room temperature for 2 hours.The reaction medium was concentrated *in vacuo* and the residue was extracted with

dichloromethane. Usual work up afforded compound **30a** (997mg, 95%) or compound **30b** (1.17 g, 90%) for two steps.

Compound **30a** : $[\alpha]_D^{20}$ -53 (c 1.22, $CHCl_3$). IR ($CHCl_3$) : 2960, 1700. ^1H NMR (250 MHz, $CDCl_3$) δ 6.57 (s, 1H, C2H), 4.60 (m, 1H, C3H), 4.33 (d, 1H, C4H, J = 5 Hz), 2.49 (dd, 1H, C5CHN, J = 7, 12.5 Hz), 2.30 (m, 2H, C5CHN, C6H), 2.20 (s, 6H, 2 NCH_3), 1.93 (m, 2H, C5H, C6H), 1.46 (s, 9H, $C(CH_3)_3$), 1.34 (s, 3H, $C(CH_3)_2$), 1.29 (s, 3H, $C(CH_3)_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.1 (C=O), 134.3 (C2), 132.9 (C1), 108.9 ($\underline{C}(CH_3)_2$), 80.4 ($\underline{C}(CH_3)_3$), 73.4, 73.0 (C3, C4), 62.2 (CH_2N), 45.9 (2 NCH_3), 34.7 (C5), 27.9 ($C(\underline{C}H_3)_3$), 27.8 ($C(\underline{C}H_3)_2$), 26.4 ($C(\underline{C}H_3)_2$), 29.4 (C6). MS (DIC, NH_3) : *m/e* 312 $[M+H]^+$.

Compound **30b** : $[\alpha]_D^{20}$ -34 (c 1.25, $CHCl_3$). IR ($CHCl_3$) : 3030, 2960, 1700, 1610. ^1H NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 5H, arom.), 6.61 (br. s, 1H, C2H), 4.62 (m, 1H, C3H), 4.42 (d, 1H, C4H, J = 5.5 Hz), 3.51 (s, 2H, NCH_2Ph), 2.66 (dd, 1H, C5CHN, J = 7, 12.5 Hz), 2.41 (m, 2H, C5CHN, C6H), 2.16 (s, 3H, CH_3N), 1.97 (m, 2H, C5H, C6H), 1.49 (s, 9H, $C(CH_3)_3$), 1.35 (s, 3H, $C(CH_3)_2$), 1.29 (s, 3H, $C(CH_3)_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.2 (C=O), 139.4 (C2), 134.5, 128.7, 128.1, 126.8 (arom.), 133.0 (C1), 108.9 ($\underline{C}(CH_3)_2$), 80.6 ($\underline{C}(CH_3)_3$), 73.4, 73.1 (C3, C4), 62.9 ($PhCH_2N$), 60.1 ($C5\underline{C}H_2N$), 42.5 (CH_3N), 34.9 (C5), 28.0 ($C(\underline{C}H_3)_3$), 27.9 ($C(\underline{C}H_3)_2$), 26.5 (C6), 23.5 ($C(\underline{C}H_3)_2$). MS (DIC, NH_3) : *m/e* 388 $[M+H]^+$.

Preparation of compound **12**. A solution of acetonide **30b** (412 mg, 1.06 mmol) and freshly distillated methyl chloroformate (88 mg, 1.2 equiv) in toluene (5mL) was stirred at 20°C for 4 hours. The reaction medium was concentrated *in vacuo* and purified by column chromatography (Pentane/AcOEt : 70:30) affording quantitatively the corresponding urethane acetonide (374mg). A solution of this compound (162 mg, 0.456 mmol) and *para*-toluene sulfonic acid (98 mg, 1.2 equiv) in *ter*-butanol was heated at 60°C for 20 hours. The reaction medium was concentrated in vacuo and treated with an aqueous solution of sodium carbonate and extracted with dichloromethane. After usual work up and purification by preparative TLC (AcOEt:MeOH: 85:15), compound **12** was isolated (113 mg, 79%).

Compound **12** : $[\alpha]_D^{20}$ -24 (c 1.13, $CHCl_3$).

Preparation of compound **31**. A solution of acetonide **30b** (431 mg, 1.11 mmol) and freshly distillated benzyl chloroformate (227 mg, 1.2 equiv) in toluene was stirred at 20°C for 4 hours affording quantitatively the corresponding urethane acetonide. Urethane acetonide previously prepared from **30b** (538 mg, 1.25 mmol) in solution in methanol-hydrochloric acid (5mL) was stirrred at room temperature for 20 hours. The reaction medium was evaporated *in vacuo* and treated with an aqueous solution of sodium carbonate (10%) and extracted with dichloromethane. Usual work up afforded quantitatively diol urethane **31** (435 mg).

Compound **31** : ^1H NMR (200 MHz, $CDCl_3$) δ 7.34 (m, 5H, arom.), 6.75 (s, 1H, C2H), 5.12 (2d, 2H, $PhCH_2CO_2$, J = 12.5 Hz), 4.21 (br. s, 1H, C3H), 4.09 (br. s, 1H, OH), 3.88 (1dd, H, C5CHN, J = 4.5, 14.5 Hz), 3.80 (m, 1H, C4H), 3.71 (s, 3H, CO_2CH_3), 3.20 (br. s, 1H, OH), 2.93 (s, 3H, NCH_3), 2.78 (dd, 1H, C5CHN, J = 4.5, 12.5 Hz), 2.22 (m, 1H, C6H), 2.09 (m, 1H, C5H), 1.94 (m, 1H, C6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9 (C=O ester), 158.0 (NC=O), 139.5 (C2), 136.1, 128.5, 128.1, 127.8

(arom.), 129.3 (C1), 68.8, 66.1 (C3, C4), 67.4 ($PhCH_2$), 51.7 ($CO_2\underline{C}H_3$), 50.8 (CH_2N), 35.6 (NCH_3), 34.9 (C5), 23.6 (C6). MS (DIC, NH_3) : *m/e* 350 $[M+H]^+$, 367 $[M+NH_4]^+$.

Preparation of compound **32**. To a solution of diol urethane **31** (269 mg, 0.77mmol) in dry DMF (4.62mL) at 0°C was added a solution of LiHMDS (1M in THF, 1.54mL, 2 equiv). After 30min. at this temperature, a solution of propargyl bromide in toluene (82µL, 1.2 equiv) was added dropwise.The reaction medium was stirred at 20°C for additonal 3 hours and poured into a mixture of ethyl acetate-sodium carbonate (aqueous solution 10%). The organic phase was washed again with a solution of sodium carbonate and after usual work up, the resulting crude product was purified by column chromatography (CH_2Cl_2:MeOH: 95:5) affording compound **32** (194 mg, 65%).

Compound **32** : IR ($CHCl_3$) : 3450, 3230, 3020, 2980, 2120, 1700 (br.). ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (br. s, 5H, arom.), 6.71 (br. 2s, 1H, C2H), 5.11 (br. s, 2H, $PhCH_2CO_2$), 4.27-4.14 (m, 3H, CH_2OC3, C3H), 4.00 (br. s, 1H, C4H), 3.72 (s, 3H, CO_2CH_3), 3.61 (dd, 1H, C5CHN, J = 9.5, 14 Hz), 3.40 (d, 1H, OH), 3.11 (dd, 1H, C5CHN, J = 5, 14 Hz), 2.99 (s, 3H, NCH_3), 2.46 (m, 1H, HCC), 2.35-1.95 (m, 3H, C5H, $C6H_2$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.7 (C=O ester), 157.0 (NC=O), 136.6, 128.5, 128.0, 127.8 (arom.), 135.1 (C2), 131.1 (C1), 79.4 ($H\underline{C}\underline{C}CH_2O$), 75.6 (C3), 75.4 ($HC\underline{C}\underline{C}H_2O$), 67.2 ($PhCH_2$), 64.1 (C4), 56.2 ($HCC\underline{C}H_2O$), 51.8 ($CO_2\underline{C}H_3$), 50.9 ($CH_2N$), 36.4 ($NCH_3$), 35.9 (C5), 24.0 (C6). MS (DIC, NH_3) : *m/e* 388 $[M+H]^+$, 405 $[M+NH_4]^+$.

Preparation of compound **33**. Radical cyclisation. A solution of compound **32** (25 mg, 65.6 µmol) and tributyltin hydride (30 µL, 2 equiv) and trace amount of AIBN was refluxed in toluene for 3 hours. The reaction medium was evaporated *in vacuo* and purified by preparative TLC (Pentane/AcOEt: 50:50) affording lactone **33** (38 mg, 91%).

Compound **33** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.36 (m, 5H, arom.), 6.03 (2d, 1H, C9H, J = 1.5, 51 Hz), 5.15 (br. s, 2H, $PhCH_2CO_2$), 4.62 (m, 1H, C5H), 4.29 (m, 3H, C6H, $C8aH_2$), 3.55 (m, 1H, C4CHN), 3.08 (m, 1H, C7H), 3.00 (m, 4H, NCH_3, C2H), 2.89 (m, 1H, C4CHN), 2.30 (m, 1H, C4H), 1.94 (m, 2H, $C3H_2$), 1.60-1.2 (m, 15H, $SnBu_3$), 1.00-0.75 (m, 12H, $SnBu_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.9 (C=O lactone), 156.4 (NC=O), 155.1 (C8), 136.5, 128.5, 128.0, 127.8 (arom.), 121.8 (C9), 79.0, 78.5 (C5, C6), 73.0 (C8a), 67.0 ($PhCH_2$), 51.2 (CH_2N), 47.6 (NCH_3), 41.3 (C2), 36.9 (C7), 32.4 (C4), 29.0 (CH_2 $SnBu_3$), 27.2 (CH_2 $SnBu_3$), 26.0 (C3), 13.6 (CH_3 $SnBu_3$), 9.8 (CH_2 $SnBu_3$). MS (DIC, NH_3) : *m/e* 648 $[M+H]^+$, 665 $[M+NH_4]^+$.

Preparation of *N*-oxide **35** and Cope elimination. A mixture of compound **30a** (69 mg, 2.21 µmol), *m*-CPBA (42mg, 1.1 equiv) and sodium hydrogenocarbonate (1.3 equiv) was stirred at 0°C for 2 hours. After usual work up the resulting crude *N*-oxide **35** in solution in toluene was refluxed for 2 hours. After evaporation *in vacuo* and purification by preparative TLC (Pentane/AcOEt: 60:40), compound **36** was isolated (29.5 mg, 50%).

Compound **36** : ^1H NMR (200 MHz, $CDCl_3$) δ 6.64 (m, 1H, C2H), 5.22 (s, 1H, C5=CH), 5.11 (s, 1H, C5=CH), 4.68 (m, 1H, C3H), 4.60 (d, 1H, C4H, J = 5.5 Hz), 3.11 (dm, 1H, C6H, J = 19.5 Hz), 2.96 (d, 1H, C6H, J = 19.5 Hz), 1.48 (s, 9H, $C(CH_3)_3$), 1.39 (s, 6H, $C(CH_3)_2$). MS (DIC, NH_3) : *m/e* 267 $[M+H]^+$, 284 $[M+NH_4]^+$.

Preparation of ammonium salt **37a**. Amine **29** (1g, 3.37 mmol) in solution in methyl iodide (5 mL) was stirred in the dark for 4 hours. Excess methyl iodide was evaporated in vacuo affording quantitatively **37a**. Compound **37a** : ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.13 (m, 2H, C7H, C8H), 3.81 (m, 1H, C3H, J = 10 Hz), 3.77 (s, 3H, CH_3N), 3.68 (s, 3H, CH_3N), 3.57 (m, 1H, C3H, J = 10 Hz), 3.50 (m, 1H, C6H), 2.36 (m, 1H, C4H), 2.23 (m, 2H, $C5H_2$), 1.52 (s, 3H, $C(CH_3)_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.74 (s, 3H, $C(CH_3)_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8 (C=O ester), 110.1 ($\underline{C}(CH_3)_2$), 83.7 ($\underline{C}(CH_3)_3$), 71.9, 70.7 (C7, C8), 63.0 (C1), 58.9, 58.6, 58.1 (C3, 2 NCH_3), 37.0 (C6), 30.0 (C4), 27.9 ($C(\underline{C}H_3)_3$), 25.0, 22.8 ($C(\underline{C}H_3)_2$), 18.6 (C5). MS (DIC, NH_3) : *m/e* 298.

Preparation of ammonium salt **37b**. Amine **29** (63 mg, 212 µmol), methoxyethyl bromide (40 µL, 414 µmol, 2 equiv) and tetrabutylammonium iodide (78 mg, 211µmol, 1 equiv) in solution in dichloromethane (2mL) was stirred for 2 hours. The reaction medium was evaporated *in vacuo* and the crude ammonium salt **37b** used directly in the following step.

Hofmann elimination. Preparation of compound **38**. Experimental condition, see: preparation of compounds **30a** and **30b**. The crude ammonium salt **37b** afforded compound **38** (30 mg, 40%) after purification by preparative TLC (Pentane:AcOEt: 10:90).

Compound **38** : IR ($CHCl_3$) : 2920, 1700. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.55 (br. s, 1H, C2H), 4.57 (m, 1H, C3H), 4.36 (d, 1H, C4H), 3.43 (2t, 2H, $NCH_2C\underline{H}_2O$, J = 1.5, 6.5 Hz), 3.32 (s, 3H, OCH_3), 2.62 (m, 1H, C5CHN), 2.55 (2t, 2H, $NC\underline{H}_2CH_2O$, J = 1.5, 6.5 Hz), 2.30 (m, 1H, C5CHN), 2.26 (s, 3H, NCH_3), 1.90 (m, 3H, C5H, $C6H_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.32 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.3 (C=O ester), 134.5 (C2), 133.0 (C1), 108.9 ($\underline{C}(CH_3)_2$), 80.6 ($\underline{C}(CH_3)_3$), 73.3, 73.0 (C4, C3), 70.8 ($NCH_2\underline{C}H_2O$), 60.2 ($N\underline{C}H_2CH_2O$), 58.8 (OCH_3), 57.7 ($C5\underline{C}H_2N$), 43.7 (NCH_3), 35.1 (C5), 28.0 ($C(\underline{C}H_3)_3$), 27.9 ($C(\underline{C}H_3)_2$), 26.5 ($C(\underline{C}H_3)_2$), 23.5 (C6). MS (DIC, NH_3) : *m/e* 356 $[M+H]^+$.

Preparation of diol **39a**. A solution of acetonide **30a** (135 mg, 0.433 mmol) and *para*-toluenesulfonic acid (99mg, 1.2 equiv) in *ter*-butanol was heated at 60°C for 20 hours. The reaction medium was evaporated *in vacuo*, treated with an aqueous solution of sodium carbonate (10%) and extracted with dichloromethane. After preparative TLC, diol **39a** was isolated (95 mg, 81%).

Preparation of diol **39b**. A solution of acetonide **38** (30 mg, 84mL) was stirred for 6 hours at room temperature in methanol saturated with hydrochloric acid (2 mL). After evaporation *in vacuo*, the residue was treated with an aqueous solution of sodium carbonate (10%) and extracted with dichloromethane affording quantitatively diol **39b** (29 mg).

Compound **39a** : IR ($CHCl_3$) : 3450, 2940, 1720. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.62 (s, 1H,C2H), 5.07 (br. s, 2H, 2 OH), 4.21 (br. s, 1H, C3H), 3.98 (br. s, 1H, C4H), 2.76 (dd, 1H, C5CHN, J = 10, 12.5 Hz), 2.20 (s, 6H, 2 NCH_3), 2.12 (m, 3H, C5CHN, C6H, C5H), 1.97 (m, 1H, C6H), 1.49 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8 (C=O ester), 137.0 (C2), 131.9 (C1), 80.4 ($\underline{C}(CH_3)_3$), 68.5, 68.0 (C3, C4), 61.5 (CH_2N), 45.7 (2 NCH_3), 34.2 (C5), 27.9 ($C(\underline{C}H_3)_3$), 25.4 (C6). MS (DIC, NH_3) : *m/e* 272 $[M+H]^+$.

Compound **39b** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.78 (br. s, 1H, C2H), 4.21 (m, 1H, C3H), 4.09 (m, 1H, C4H), 3.70 (s, 3H, CO_2CH_3), 3.44 (m, 2H, $NCH_2C\underline{H}_2O$), 3.31 (s, 3H, $CH_2OC\underline{H}_3$), 2.81 (dd, 1H,

C5CHN, J = 9.5, 12.5 Hz), 2.57 (m, 2H, $NC\underline{H}_2CH_2O$), 2.29 (m, 1H, C5CHN), 2.25 (m, 4H, NCH_3, C6H), 2.15 (m, 1H, C5H), 2.04 (m, 1H, C6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.2 (C=O ester), 138.4 (C2), 130.3 (C1), 70.4, 68.7 (C3, C4), 67.7 ($NCH_2\underline{C}H_2O$), 59.7 ($N\underline{C}H_2CH_2O$), 58.7 ($CH_2O\underline{C}H_3$), 57.5 (CH_2N), 51.8 ($CO_2\underline{C}H_3$), 43.1 (NCH_3), 34.1 (C5), 25.7 (C6). MS (DIC, NH_3) : *m/e* 274 $[M+H]^+$.

Preparation of compounds **40a** and **41a**. Experimental condition, see: preparation of compound **32**. Compound **39a** (48 mg, 0.177mmol) afforded compounds **40a** (12.5 mg, 23%) and **41a** (10.5 mg, 17%) after preparative TLC (Pentane:AcOEt: 50:50).

Compound **40a** : ^1H NMR (250 MHz, $CDCl_3$) δ 6.66 (br. s, 1H, C2H), 4.36 (t, 2H, CH_2O, J = 2.5 Hz), 4.20 (m, 1H, C3H), 4.11 (m, 1H, C4H), 3.25 (m, 1H, OH), 2.78 (dd, 1H, C5CHN, J = 7.5, 12.5 Hz), 2.45 (1H, t, HCC, J = 2.5 Hz), 2.34-1.90 (4H, m, C5CHN, C5H, $C6H_2$), 2.24 (6H, s, 2 NCH_3), 1.42 (9H, s, $C(CH_3)_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.4 (C=O ester), 134.2 (C2), 132.1 (C1), 80.1 ($\underline{C}(CH_3)_3$), 78.7, 79.4 ($H\underline{C}C\text{-}CH_2O$), 75.4 ($HC\underline{C}CH_2O$), 74.7 (C3), 65.3 (C4), 60.8 ($HCC\underline{C}H_2O$), 57.4 (CH_2N), 45 (2 NCH_3), 35.5 (C5), 28.0 ($C(\underline{C}H_3)_3$), 25.3 (C6). MS (DIC, NH_3) : *m/e* 310 $[M+H]^+$.

Compound **41a** : ^1H NMR (250 MHz, $CDCl_3$) δ 6.66 (br. s, 1H, C2H), 4.40 (d, 2H, CH_2O, J = 2.5 Hz), 4.32 (m, 3H, C3H, CH_2O), 4.13 (m, 1H, C4H), 2.63 (dd, 1H, C5CHN, J = 8, 12.5 Hz), 2.43 (2t, 2H, 2 HCC, J = 2.5 Hz), 2.22 (m, 7H, 2 NCH_3, C5CHN), 2.07 (m, 2H, C5H, C6H), 1.81 (m, 1H, C6H), 1.44 (s, 9H, 3 CH_3). MS (DIC, NH_3) : *m/e* 292, 348 $[M+H]^+$.

Preparation of compound **40b**. Experimental condition, see: preparation of compound **32**. Diol **39b** afforded compound **40b** (55%).

Compound **40b** : ^1H NMR (250 MHz, $CDCl_3$) δ 6.79 (br. s, 1H, C2H), 4.39 (d, 2H, $HCCC\underline{H}_2O$, J = 2.5 Hz), 4.26 (br. s, 1H, C3H), 4.22 (br. s, 1H, C4H), 3.75 (s, 3H, $CO_2\underline{C}H_3$), 3.50 (t, 2H, $NCH_2C\underline{H}_2O$, J = 6.5 Hz), 3.36 (s, 3H, $CH_2O\underline{C}H_3$), 2.81 (dd, 1H, C5CHN, J = 9.5, 12.5 Hz), 2.61 (m, 2H, $NC\underline{H}_2CH_2O$), 2.48 (t, 1H, HCC, J = 2.5 Hz), 2.31 (s, 3H, NCH_3), 2.40-1.90 (m, 4H, $C6H_2$, C5H, C5CHN). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.3 (C=O ester), 135.3 (C2), 131.8 (C1), 79.6 ($H\underline{C}CCH_2O$), 75.3 (C3), 74.9 ($HC\underline{C}CH_2O$), 70.7 ($NCH_2\underline{C}H_2O$), 66.8 (C4), 59.9 ($N\underline{C}H_2CH_2O$), 58.8 ($CH_2O\underline{C}H_3$), 57.4 (CH_2N), 57.0 ($HCC\underline{C}H_2O$), 51.8 ($CO_2\underline{C}H_3$), 43.5 (NCH_3), 34.7 (C5), 25.7 (C6). MS (DIC, NH_3) : *m/e* 312 $[M+H]^+$.

Preparation of diacetate **42**. A solution of diol **31** (316 mg, 0.9mmol) in a mixture of pyridine-acetic acid (3:1, 3mL) and trace amount of 4-dimethylaminopyridine was stirred at 20°C for 2 hours. After evaporation *in vacuo*, the reaction medium was treated with brine and extracted with diethylether. After usual work up, the crude residue was purified by column chromatography (Pentane/AcOEt: 50:50) affording diacetate **42** (368 mg, 94%).

Compound **42** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5H, arom.), 6.57 (br. s, 1H, C2H), 5.51 (m, 1H, C3H), 5.31 (br. s, 1H, C4H), 5.10 (br. s, 2H, $PhCH_2CO_2$), 3.73 (s, 3H, CO_2CH_3), 3.36 (m, 2H, $C5CH_2N$), 2.87 (2s, 3H, NCH_3), 2.50-2.10 (m, 3H, C5H, $C6H_2$), 2.04 (br. s, 3H, CH_3CO_2), 1.99 (br. s, 3H, CH_3CO_2). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.6, 169.9 ($C3O\underline{C}{=}O$, $C4O\underline{C}{=}O$), 166.1 ($C1\underline{C}{=}O$), 156.3 (NC=O), 136.5, 128.4, 127.8, 127.7 (arom.), 134.3 (C2), 132.0 (C1), 69.2 (C3), 67.4 ($PhCH_2$),

65.8 (C4), 51.9 (OCH_3), 50.1 (CH_2N), 35.2 (NCH_3), 34.6 (C5), 24.3 (C6), 20.6 (2 $\underline{C}H_3CO_2$). MS (DIC, NH_3) : *m/e* 434 $[M+H]^+$, 451 $[M+NH_4]^+$.

Preparation of compounds **43a** and **43b**. To a stirred solution of *para*-methoxythiophenol (4 equiv) in THF was added a solution of LiHMDS (1M in THF, 4 equiv) at room temperature. A solution of diacetate **42** (187 mg, 0.431 mmol) in THF (1 mL) was added to the THF solution of thiophenate. After 10 minutes, the reaction mixture was evaporated *in vacuo*, extracted with dichloromethane and washed successively with water and brine. After purification by preparative TLC (Pentane/AcOEt: 50:50), compounds **43a** and **43b** were isolated.

Compound **43a** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.29 (m, 7H, $C_6\underline{H}_5CH_2CO_2$ (5H), $MeOC_6\underline{H}_4S$ (2H)), 6.82 (d, 2H, $OC_6\underline{H}_4S$, J = 9.5 Hz), 5.25 (br. s, 1H, C4H), 5.01 (m, 2H, $PhCH_2$), 4.48 (m, 1H, C3H, J = 12.5 Hz), 3.77 (s, 6H, CH_3OPhS, $C1CO_2CH_3$), 3.26 (m, 1H, C2H), 3.09 (m, 2H, $C5CH_2N$), 2.77 (br. s, 3H, NCH_3), 2.44 (m, 1H, C1H), 2.10-1.95 (m, 6H, 2 CH_3CO_2), 1.90-1.6 (m, 3H, C5H, $C6H_2$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.0, 170.1(2c) (CO_2CH_3, C3O$\underline{C}$=O, C4O$\underline{C}$=O), 160.3 (NC=O), 156.1, 137.9, 119.8, 114.4 (OPhS), 136.4, 128.3, 127.8, 127.7 (C_6H_5), 67.1 ($PhCH_2$), 55.1 ($\underline{C}H_3OPhS$), 52.0 ($CO_2\underline{C}H_3$), 50.0 (CH_2N), 72.3, 68.4 (C3, C4), 46.9 (C2), 46.8 (C1), 36.3 (C5), 34.8 (NCH_3), 27.6 (C6), 20.7 (2 $\underline{C}H_3CO_2$). MS (DIC, NH_3) : *m/e* 474 $[M+H]^+$, 491 $[M+NH_4]^+$.

Compound **43b** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 7H, $C_6\underline{H}_5CH_2CO_2$ (5H), $MeOC_6\underline{H}_4S$ (2H)), 6.77 (d, 2H, $OC_6\underline{H}_4S$, J = 9.5 Hz), 5.29 (br. s, 1H, C4H), 5.23-4.88 (m, 3H, $PhCH_2CO_2$, C3H, J = 12 Hz), 3.90 (m, 1H, C2H), 3.74 (s, 3H, $C1CO_2CH_3$), 3.35 (dd, 1H, C5CHN, J = 8, 14 Hz), 3.25 (s, 3H, CH_3OPhS), 3.13 (dd, 1H, C5CHN, J = 5.5, 14 Hz), 2.88 (2s, 3H, NCH_3), 2.74 (m, 1H, C1H), 2.20-1.90 (m, 8H, 2 CH_3CO_2, C5H, $C6H_2$), 1.70 (1H, m, C6H). MS (DIC, NH_3) : *m/e* 474 $[M+H]^+$, 491 $[M+NH_4]^+$.

Oxidation of **43a** to **44** with SO_2Cl_2. To a stirred solution of **43a** (26 mg, 45.4 mmol) in dichloromethane was added dropwise at 0°C a solution of sulfuryl chloride (20 µL, 249 µmol, 5 equiv) in dichloromethane (500 µL). The reaction medium was stirred at the same temperature for 2 hours and evaporated *in vacuo*. The residue was extracted with dichloromethane and washed with an aqueous solution of sodium hydrogenocarbonate. After usual work up, the crude product was purified by preparative TLC (Heptane/AcOEt: 20:80) and afforded **44** (20 mg, 73%) as a mixture of 2 isomers.

Compound **44** : ^1H NMR (250 MHz, $CDCl_3$) δ 7.48 (d, 2H, OC_6H_4S, J = 8.5 Hz), 7.31 (m, 5H, C_6H_5), 6.99 (d, 2H, OC_6H_4S, J = 8.5 Hz), 5.30 (br. s, 1H, C4H), 5.07 (m, 3H, $PhCH_2$, C3H), 3.85, 3.79 (2 x s, 2 x 3H, CH_3OPhS, $C1CO_2CH_3$), 3.62 (br. t, 1H, C2H, J = 12.5 Hz), 3.17 (m, 2H, $C5CH_2N$), 3.00-2.75 (m, 4H, NCH_3, C1H), 2.20-1.55 (m, 9H, 2 CH_3CO_2, C5H, $C6H_2$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.3, 169.9 (2C) (CO_2CH_3, C3O$\underline{C}$=O, C4O$\underline{C}$=O), 161.5, 136.5, 125.8, 114.4 (OC_6H_4S), 156.3 (NC=O), 132.5, 128.4, 127.8, 127.7 (C_6H_5), 68.4, 68.2 (C3, C4), 67.3 ($PhCH_2$), 60.9 (C2), 55.5 (CH_3OPhS), 52.6 ($CO_2\underline{C}H_3$), 49.8 (C1), 41.7 (CH_2N), 36.4 (C5), 36.0 (NCH_3), 27.2 (C6), 20.6 (2 $\underline{C}H_3CO_2$). MS (DIC, NH_3) : *m/e* 434, 451.

Treatment of the mixture of **43a** and **43b** with *m*-CPBA. Preparation of sulfoxides **44**. A solution of the mixture of **43a** and **43b** (28, 6 mg, 0.05 mmol) and *m*CPBA (8.7 mg, 0.05 mmol) in dichloromethane (0.5 mL) was stirred at 0°C for 30 min. The reaction medium was diluted with dichloromethane (5 mL) and

washed with an aqueous solution of sodium hydrogenocarbonate (10%). Usual treatment afforded sulfoxides **44** (23 mg, 86%) as a mixture of diastereomers. Purification by preparative TLC (AcOEt/Heptane: 60:40) afforded pure isomers.

Compound **44** (less polar isomer) : This compound was identical with sulfoxide **44** prepared by the previous route.

Compound **44** (more polar isomer) : ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 (d, 2H, OC_6H_4S, J = 8.5 Hz), 7.31 (m, 5H, C_6H_5), 7.00 (d, 2H, OC_6H_4S, J = 8.5 Hz), 5.36 (br. s, 1H, C4H), 5.10 (m, 3H, $PhCH_2$, C3H), 3.84 (s, 3H, $C1CO_2CH_3$), 3.68 (br. t, 1H, C2H, J = 12.5 Hz), 3.46 (s, 3H, CH_3OPhS), 3.17 (m, 2H, $C5CH_2N$), 2.90 (m, 4H, NCH_3, C1H), 2.20-1.95 (6H, m, 2 CH_3CO_2), 2.20-1.55 (m, 3H, C5H, $C6H_2$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.3, 170.0, 168.9 (CO_2CH_3, C3O<u>C</u>=O, C4O<u>C</u>=O), 161.5, 136.5, 125.8, 114.5 (OC_6H_4S), 156.6 (NC=O), 132.1, 128.4, 127.8, 126.8 (C_6H_5), 71.2, 68.2 (C3, C4), 67.3 ($PhCH_2$), 61.0 (C2), 55.4 (CH_3OPhS), 52.6 (CO_2CH_3), 49.8 (C1), 41.7 (CH_2N), 35.9 (C5), 34.5 (NCH_3), 27.3 (C6), 20.5 (2 <u>C</u>H_3CO_2). MS (DIC, NH_3) : *m/e* 434, 451.

Preparation of compound **45**. Trifluoroacetic anhydride (10 µL, 2.1 equiv.) was added to a solution of sulfoxides **44** (20 mg, 34 µmol) and 2,6-lutidine (4µL, 1 equiv.) in dichloromethane (0.2mL) at 0°C. The resulting mixture was stirred at 20°C for 2 hours, evaporated *in vacuo* and the residue was purified by preparative TLC (AcOEt/Heptane: 60:40) affording **45** (11 mg, 56%).

Compound **45** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29 (m, 7H, $C_6\underline{H}_5CH_2CO_2$ (5H), $MeOC_6\underline{H}_4S$ (2H)), 6.78 (d, 2H, $OC_6\underline{H}_4S$, J = 9.5 Hz), 5.37 (br. s, 1H, C4H), 5.25 (m, 1H, C3H), 5.09 (m, 2H, $PhCH_2$), 3.77 (2s, 6H, CH_3OPhS, $C1CO_2CH_3$), 3.25 (m, 2H, $C5CH_2N$), 2.91 (2s, 3H, NCH_3), 2.65-2.22 (m, 3H, C5H, $C6H_2$), 2.08 (2s, 3H, CH_3CO_2), 1.85 (2s, 3H, CH_3CO_2). MS (DIC, NH_3) : *m/e* 156, 451, 572 $[M+H]^+$, 589 $[M+NH_4]^+$.

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11) Examination of coupling constant C4H-C5H J = 11Hz in compound **13** let us to attribute *trans* configurations at the ring junction and the absolute configurations at C3 and C4 in diols **11** and **12**.

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16) 10% of the corresponding nitrate at C3 was also obtained in this reaction.

17) Rich, R.H.; Lawrence, B.M.; Bartlett, P.A. *J. Org. Chem.* **1994**, *59*, 693-694.

18) a) see reference 3c. b) Crimmins, M. T.; Hollis, Jr. W.G.; Lever, J.G. *Tetrahedron Lett.* **1987**, *28*, 3647-3650.

19) The previously observed base induced fragmentation was not possible with acetonide **29**. The C-N bond in that case is not in an allylic position like in compounds **9a-9b**.

20) A correlation between the two approachs was achieved by sequential treatment of **30b** with methyl chloroformate and TsOH, H_2O, THF affording a compound identical with the *cis* diol **12.**

21) Avermectin numbering.

22) These two strategies afforded *cis* diols **11** or **31** of reverse absolute configurations at C3 and C4 if (+)-camphor is used as chiral auxiliary. In a total synthesis of Avermectin antibiotics, the use of (+) or (-)-camphor will allow the control of absolute configuration in both cases.

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