Tin Triflate Catalysed Selective Synthesis of *N,N'*-Unsymmetrically Substituted *N*-(Hydroxyclovanyl)-*N'*-aryl Acetamidines

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Dedicated to Professor James R. Hanson on his 65th birthday.

Abstract: The unsymmetrically substituted amidines **6a–d** have been prepared in one step from caryophyllene oxide (**2**), aromatic amines (**4a–c**, **5**), and tin triflate as catalyst, in refluxing MeCN.

Key words: natural products, cyclization, epoxides, Lewis acids, amidines

Amidines are compounds widely used as antibiotics, diuretics, antiphlogistic drugs, anthelmintics and wide-spectrum acaricides.[1] They are also valuable synthons for the preparation of heterocyclic compounds,[2,3] and are structural features in many natural substances.[4]

The direct synthesis of amidines from nitriles and amines can be achieved only if nitriles contain electron-withdrawing groups (e.g. Cl_3CCN).[5] Unactivated nitriles are most commonly transformed in the first step into imidate ester salts, which are in turn reacted with amines (Pinner synthesis),[6–8] to best give *N*-monosubstituted or *N,N*-disubstituted amidines.

N,N'-Disubstituted amidines can be prepared from nitriles using milder methods,[9,10] or by reaction of amides with primary and secondary amines.[11,12] These methods are problematic for the preparation of unsymmetrically substituted amidines, as symmetrical amidines can be formed as side products.[13] Alternatively, amidines with higher substitution, can be prepared by *N*-alkylation of simpler amidines.[14]

Hence, it is not trivial to prepare *N,N'*-unsymmetrically substituted amidines and would be desirable to develop novel methods of synthesis. Additionally, we are interested in the synthesis of derivatives of the sesquiterpene clovan-2α,9β-diol (**1a**), as environmentally friendly and selective inhibitors of the fungus *Botrytis cinerea*. 2-Alkoxyclovane-9α-ol derivatives **1** (Figure 1),[15] present a structural similarity to the proposed key intermediate **3**[16] in the biosynthesis[17] of the phytotoxic[18] botryane metabolites produced by the fungus *B. cinerea*, and they have been shown to inhibit the growth of this fungus.[19] Some of the more active alkoxyclovanols **1** present nitrogen atoms in the side chain at C-2.[15b] Further research requires the preparation of novel derivatives with clovane skeleton, with nitrogen atoms directly attached at C-2.

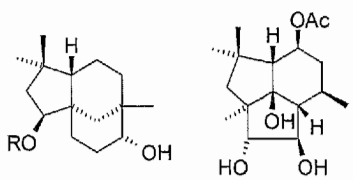

Figure 1

The cleavage of epoxides by amines can be carried out by several methods.[20–22] $Sn(OTf)_2$ has been described as catalyst in the opening of *meso* epoxides by aromatic amines[23] and was selected for our purpose. This paper deals with the use of $Sn(OTf)_2$ as a catalyst in the selective, one-pot synthesis of *N*-(hydroxyclovanyl)-*N'*-arylacetamidine derivatives (**6a–d**).

The treatment of caryophyllene oxide (**2**) with several anilines (**4a–c**) or 2-aminopirimidine (**5**), in acetonitrile, at 80 °C and catalysed by $Sn(OTf)_2$,[24] lead to compounds **6a–d**,[25] (Table 1) which were characterised by their MS and NMR spectra. For instance, the major product obtained when aniline (**4a**) was used as starting material (compound **6a**) (47%) showed signals in its ^1H NMR at $\delta_H = 4.18$ [dd, $J = 5.5$, 11.3 Hz, 1 H, CHN=C(CH_3)NHPh], 3.27 ppm [br s, CH(OH)], 1.12 ppm (s, 3 H), 1.00 ppm (s, 3 H), 0.96 ppm (s, 3 H), assigned to H-2α, H-9β, H-14′, H-13′, and H-15′, respectively. Nuclear Overhauser enhancement and 2D COSY studies led to a full assignment of the sesquiterpenic part of the ^1H NMR spectrum and are fully consistent with the stereochemistry. These data were very similar to that of the known clovan-2β,9α–diol (**1a**)[26] and its 2β-alkoxyclovane-9α-ol derivatives **1**.[15] In addition to that, there are some additional signals in the ^1H NMR at δ_H 7.50 = (t, $J = 7.3$ Hz, 2 H), 7.43 ppm (t, $J = 7.3$ Hz, 1 H), 7.34 ppm (t, $J = 7.3$ Hz, 2 H), and 2.15 ppm [s, $H_3CC(=N)NH$, 3 H], assigned to H-3″ and H-5″, H-4″, H-2″ and H-6″ and finally to H-2, respectively. This, together with the existence of a signals in the ^{13}C NMR at δ_C = 164.83 [s, $H_3CC(=N)NH$] and 18.64 ppm [q, $H_3CC(=N)NH$], assigned to C-1 and C-2, respectively, suggest the existence of an *N*-alkyl-*N'*-phenyl acetamidine moiety. Further support for a fused structure of *N*-(hydroxyclovanyl)-*N'*-phenyl acetamidine was drawn

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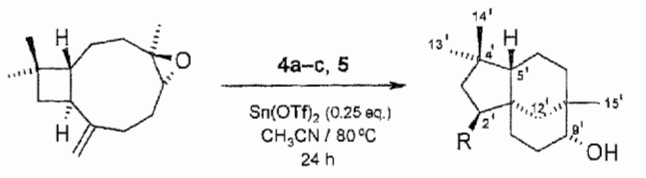
Table 1 $Sn(OTf)_2$ Catalysed Selective Synthesis of *N*-(Hydroxyclovanyl)-*N'*-aryl Acetamidines (**6**)



2 **6a–d** **7a–d**

4 or **5**	**6**	Amines (**7**)
Aniline (**4a**)	**6a** R = (47%)	**7a** R = (5%)
p-Methoxyaniline (**4b**)	**6b** R = (42%)	**7b** R = (2%)
p-Bromoaniline (**4c**)	**6c** R = (39%)	–
2-Aminopyrimidine (**5**)	**6d** R = (37%)	–

from the EIMS of **6a**. The EIMS of **6a** showed peaks at *m/z* 354 and *m/z* 262, which were assigned to $[M^+]$ and $[M^+ - PhNH_2]$, respectively. Noteworthy is that all the compounds prepared of this series (**6a–d**) showed a peak at *m/z* 262 which can be attributed to the loss of the amine used for its preparation (**4a–c**, **5**) from the molecular ion. These data are consistent with the structure proposed for **6a** as *N*-(9α-hydroxyclovan-2β-yl)-*N'*-phenyl acetamidine.

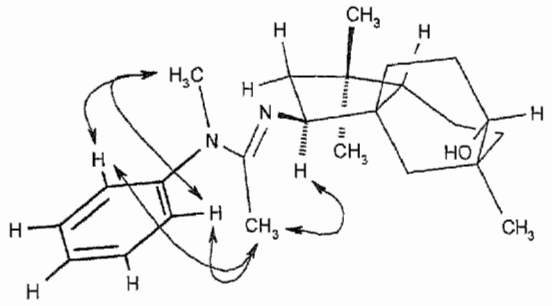


Figure 2 Selected NOESY correlations for compound **8**.

In order to support the structures proposed for compounds **6a–d**, the preparation of a suitable derivative was needed. For instance, the treatment of compound **6a** with MeI and an excess of K_2CO_3 in acetone for 48 h, led to the monomethylated compound **8**, which was characterized by MS and NMR techniques.[27] The assignations in the ^1H NMR and ^{13}C NMR and the regio and stereochemistry of the compound were supported by the HMBC,[27] and NOESY spectra (see Figure 2). This allows the assignation of compound **8** as *N*-(9α-hydroxyclovan-2β-yl)-*N'*-methyl-*N'*-phenyl acetamidine, which in turn supports the assignation of **6a–d** as a series of fused clovane phenyl acetamidines. The regioselectivity of the methylation is consistent with that observed for the alkylation of alkyl phenyl amidines.[28] To our knowledge, this is the first preparation of unsymmetrically substituted amidines containing a clovane moiety.

The rationalization of these results follows from the known preference of caryophyllene oxide (**2**) to give intramolecular epoxide opening and rearrangement products,[15] due to the special disposition of the epoxide, which precludes a direct intermolecular attack.[29] Under the previously described conditions, $Sn(OTf)_2$ produces the activation of the nitrile by the cleavage and rearrangement of caryophyllene oxide (**2**) and subsequent attack on the resulting nitrilium intermediate by amines, in an extension of the methodology of Fuks for the synthesis of *N,N'*-disubstituted amidines.[8f]

Compounds **7a,b** were isolated as minor compounds. The structure for **7a** and **7b** were established by MS and NMR techniques. These data were very similar to that of the known clovan-2β,9α-diol (**1a**)[26] and its 2β-alkoxyclovane-9α-ol derivatives **1**,[15] and led to the assignation of the structure of compound **7a** as 2β-phenylaminoclovan-9α-ol and compound **7b** as 2β-(*p*-methoxyphenylamino)clovan-9α-ol.

Following the same procedure, several other non-aromatic amines (*n*-propylamine, *n*-butylamine, allylamine and *tert*-butylamine) were tried as precursors of acetamidines. None of them gave any reaction products, neither with a clovane moiety nor without it, which suggests a deactivation of the catalyst by coordination of these amines to the Lewis acid.[23]

In conclusion, we present here a novel, one-pot, catalytic preparation of *N*-(hydroxyclovanyl)-*N'*-aryl acetamidines, which yields optically active compounds with an amidine moiety, from a enantiomerically pure epoxide precursor as caryophyllene oxide (**2**). Work is in progress to extend this reaction to other epoxides, nitriles and amines.

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(24) Typical Experimental Procedure: To a magnetically stirred solution of caryophyllene oxide (**2**) (450 mg, 2.045 mmol) and aniline (**4a**) (353 mg, 8.18 mmol) in anhyd MeCN (8 mL), $Sn(OTf)_2$ (351 mg, 0.51 mmol) was added and the reaction mixture was heated to 80 °C. After 24 h., once compound **2** was consumed (TLC), the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel to yield the amidine **6a** (340 mg, 47%) and the amine **7a** (36 mg, 5%).

(25) Selected physical data for compound **6a**: $[\alpha]_D$ +16.6 (c 9.2 mg/mL, MeOH). Selected physical and spectroscopic data for compound **6b**: $[\alpha]_D$ –3.2 (c 43.3 mg/mL, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 0.86 (s, 3 H, H_3-15′), 0.89 (s, 3 H, H_3-13′α), 1.01 (s, 3 H, H_3-14′β), 1.20 (d, $J_{12'a\text{-}12'b}$ = 11.0 Hz, 1 H, H-12′a), 1.42 (d, $J_{12'b\text{-}12'a}$ = 11.0 Hz, 1 H, H-12′b), 1.62 (dd, $J_{3'\alpha\text{-}2'\alpha}$ = 6.6 Hz, $J_{3'\alpha\text{-}3'\beta}$ = 11.4 Hz, 1 H, H-3′α), 1.70 (t, $J_{3'\beta\text{-}2'\alpha} = J_{3'\beta\text{-}3'\alpha}$ = 11.4 Hz, 1 H, H-3′β), 1.94 (m, 1 H, H-10′b), 2.04 (s, 3 H, H_3-2), 3.16 (br s, 1 H, H-9′β), 3.72 (s, 3 H, H_3-1‴), 4.04 (dd, $J_{2'\alpha\text{-}3'\beta}$ = 11.40 Hz, $J_{2'\alpha\text{-}3'\alpha}$ = 6.6 Hz, 1 H, H-2′α), 6.92 (d, $J_{3''\text{-}2''} = J_{5''\text{-}6''}$ = 9.0 Hz, 2 H, H-3″, H-5″), 7.19 (d, $J_{2''\text{-}3''} = J_{6''\text{-}5''}$ = 9.0 Hz, 2 H, H-2″, H-6″). ^{13}C NMR (100 MHz, CD_3OD): δ = 18.60 (c, C-2), 21.56 (t, C-6′), 24.62 (c, C-13′), 26.54 (t, C-10′), 28.79 (t, C-11′), 29.01 (c, C-15′), 30.91 (c, C-14′), 33.92 (t, C-7′), 36.01 (s, C-8′), 36.62 (t, C-12′), 39.07 (s, C-4′), 45.29 (t, C-3′), 47.03 (s, C-1′), 51.91 (d, C-5′), 56.07 (c, C-1‴), 61.97 (d, C-2′), 75.13

(d, C-9′), 115.92 (2C, d, C-3″, C-5″), 128.65 (s, C-1″), 129.50 (2C, d, C-2″, C-6″), 161.34 (s, C-4″), 165.71 (s, C-1). MS (EI): *m/z* (rel. int.) = 384 (87) [M⁺], 369 (22) [M – 15]⁺, 325 (41), 262 (33). Compound **6c**: $[\alpha]_D$ +12.9 (c 20 mg/mL, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ 0.92 (s, 3 H, H_3-15′), 0.94 (s, 3 H, H_3-13′α), 1.05 (s, 3 H, H_3-14′β), 1.74 (m, 1 H, H-12′b), 1.77 (s, 3 H, H_3-2), 2.00 (m, 1 H, H-10′b), 3.22 (br s, 1 H, H-9′β), 4.29 (m, 1 H, H-2′α), 6.70 (d, $J_{2''-3''} = J_{6''-5''} = 8.4$ Hz, 2 H, H-2″, H-6″), 7.33 (d, $J_{3''-2''} = J_{5''-6''} = 8.4$ Hz, 2 H, H-3″, H-5″). ^{13}C NMR (100 MHz, CD_3OD): δ = 18.08 (c, C-2), 21.76 (t, C-6′), 25.02 (c, C-13′), 26.79 (t, C-10′), 29.04 (t, C-11′), 29.18 (c, C-15′), 31.31 (c, C-14′), 34.46 (t, C-7′), 35.93 (s, C-8′), 37.19 (t, C-12′), 38.40 (s, C-4′), 45.74 (t, C-3′), 46.68 (s, C-1′), 52.11 (d, C-5′), 59.40 (d, C-2′), 75.78 (d, C-9′), 115.64 (s, C-4″), 126.18 (d, 2 C, C-2″, C-6″), 132.63 (d, C-3″, C-5″), 152.51 (s, C-1″), 159.51 (s, C-1). MS (EI): *m/z* (rel. int.) = 434(48) [M + 2]⁺, 432 (47) (M⁺), 375 (23), 373 (22), 353 (41) [M – 79]⁺, 292 (27), 262(46). Compound **6d**: $[\alpha]_D$ +98.4 (c = 17 mg/mL, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.96 (s, 3 H, H_3-15′), 1.00 (s, 3 H, H_3-13′), 1.14 (s, 3 H, H_3-14′), 1.86 (2 H, H-3′α, H-3′α), 2.08 (m, 1 H, H-10′b), 2.59 (m, 3 H, H_3-2), 3.25 (sa, 1 H, H-9′β), 4.02 (dd, $J_{2'\alpha-3'\beta} = 11.1$ Hz, $J_{2'\alpha-3'\alpha} = 6.3$ Hz, 1 H, H-2′α), 7.40 (t, $J_{4''-3''} = J_{4''-5''} = 5.0$ Hz, 1 H, H-4″), 8.81 (d, $J_{3''-4''} = J_{5''-4''} = 5.0$ Hz, 2 H, H-3″, H-5″). ^{13}C NMR (100 MHz, CD_3OD): δ = 17.81 (c, C-2), 21.60 (t, C-6′), 24.77 (c, C-13′), 26.64 (t, C-10′), 28.89 (c, C-15′), 29.01 (t, C-11′), 30.91 (c, C-14′), 33.83 (t, C-7′), 36.03 (s, C-8′), 36.46 (t, C-12′), 39.49 (s, C-4′), 46.34 (t, C-3′), 46.61 (s, C-1′), 51.87 (d, C-5′), 65.85 (d, C-2′), 75.14 (d, C-9′), 119.82 (d, C-4″), 159.16 (s, C-1″), 159.69 (d, 2 C, C-3″, C-5″), 165.96 (s, C-1). HMBC cross peaks (selected): C-1 → H-2′α, H_3-2. MS (EI): *m/z* (rel. int.) = 357 (27) [M + 1]⁺, 339 (40) [M + 1 – 18]⁺, 263(24)

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(27) Selected physical and spectroscopic data for compound **8**: $[\alpha]_D$ +14.0 (*c* 2.2 mg/mL, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (s, 3 H, H_3-13′α), 0.95 (s, 3 H, H_3-15′), 1.06 (s, 3 H, H_3-14′β), 1.66 (dd, *J* = 10.8, 11.6 Hz, 1 H, H-3′β), 1.76 (m, 1 H, H-11′b), 1.77 (s, 3 H, H_3-2), 2.00 (m, 1 H, H-10′b), 3.24 (s, 3 H, H_3-1‴), 3.31 (br s,1 H, H-9′β), 3.46 (dd, *J* = 6.0, 10.8 Hz, 1 H, H-2′α), 7.08 (d, *J* = 7.6 Hz, 2 H, H-2″, H-6″), 7.17 (t, *J* = 7.6 Hz, 1 H, H-4″), 7.32 (d, *J* = 7.6 Hz, 2 H, H-3″, H-5″). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.06 (q, C-2), 21.02 (t, C-6′), 25.51 (q, C-13′α), 26.45 (t, C-10′), 28.12 (t, C-11′), 28.50 (q, C-15′), 31.38 (q, C-14′β), 33.45 (t, C-7′), 34.95 (s, C-8′*), 36.76 (t, C-12′), 38.62 (s, C-1′*), 39.67 (q, C-1‴), 46.09 (s, C-4′*), 47.46 (t, C-3′), 50.75 (d, C-5′), 67.55 (d, C-2′), 75.41 (d, C-9′), 125.41 (d, C-4″), 126.75 (d, 2 C, C-2″, C-6″), 129.15 (d, 2 C, C-3″, C-5″), 147.17 (s, C-1″), 156.02 (s, C-1). HMBC cross peaks(selected): C-1 → H_3-1‴, H-2′α, H_3-2; C-1″ → H_3-1‴, H-3″, H-5″. MS (EI): *m/z* (rel. int.) = 368 [M]⁺(10), 353 [M – 15]⁺(5), 262 (20).

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