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Keywords

CMMB

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Studies on the Synthesis of Croomine: Synthesis of the Tricyclic B,C,D-Ring Core Structure

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Abstract: A convergent and asymmetric synthesis of the tricyclic B,C,D-ring core structure of croomine has been achieved, using aminolysis reactions of chiral vinyl epoxides and the RCM reaction

Key words: oxazolindone, pyrrolidine, ring-closing metathesis, azepine, *Stemona* alkaloid.

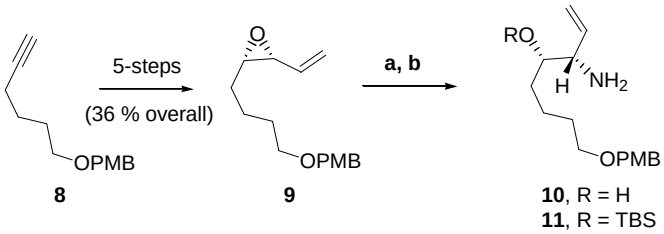
The *Stemona* group of alkaloids includes more than 40 different natural products that have been structurally classified into five different groups.[1] The pyrrolo[1,2-*a*]azepine (1-azabicyclo[5.3.0]decane) nucleus is common to all compounds in these groups. A few of these alkaloids do not fit these five structural groups and have a more complex bridged structure or ring structures that most likely arise from initial oxidative cleavage of the pyrrolo[1,2-*a*]aze

pine ring system.[1] In 2003 we reported the structure of stemocurtisine, the first example of a *Stemona* alkaloid with a pyrido[1,2-*a*]azepine A,B-ring system, isolated from the roots of *S. curtisii*.[2] Later in that year Hofer and Greger reported the isolation of four other *Stemona* alkaloids with the pyrido[1,2-*a*]azepine A,B-ring system plus stemocurtisine.[3] These alkaloids represent a new and sixth structural group for *Stemona* alkaloids. Extracts of the roots of *Stemona* species have been used in traditional Chinese medicine for the treatment of various respiratory diseases and as anthelmintic agents for domestic animals.[1] The biological activities and the structural diversity and relative complexity of these alkaloids has attracted the attention of many synthetic chemists. Their efforts have resulted in the total synthesis of several *Stemona* alkaloids[4] and the publication of model synthetic studies.[5]

We report here our efforts to develop a convergent synthesis of the tricyclic B,C,D-ring core structure of croomine (**1**) based on the retro-synthetic analysis shown in Scheme 1. Our analysis suggested that the A and D rings could be prepared by an oxidative lactonization reaction of the tetrol **2**, while the B-ring could be secured *via* a *N*-alkylation reaction. Compound **2** could be obtained from the diene **3** *via* a ring-closing metathesis reaction.[6,7] The diene **3** should be available from an epoxide-aminolysis reaction between the vinyl epoxides **4** or **7** and the allylic amines **5** and **6**, respectively.[6,8,9]

As model studies to test the viability of our proposed synthesis we have prepared the chiral allylic amine **11**, a structurally simpler analogue of **6**, and the vinyl epoxide **12**, the nor-methyl analogue of **7**, and used them as building blocks to prepare a molecule having the tricyclic B,C,D-ring core structure of croomine (**1**). Compound **11** was prepared from the chiral *cis*-epoxide **9** (ee 92-94%), which was readily available in 5 steps (38% overall) from the known PMB protected 5-hexyn-1-ol **8**[10] using chemistry already described by us (Scheme 2).[8,9] Aminolysis of **9** as a suspension in aqueous ammonia (28%) in a sealed Teflon vessel with heating in a microwave reactor (Milestone, ETHOS SEL microwave labstation)[6] at 110°C for 30 min, with strict temperature control, gave regioselectively, the amino alcohol **10** in 98% yield which was converted to its corresponding *O*-TBS ether **11** in 85% yield as a single diastereomer (Scheme 2). The chiral epoxide **12** was as previously described from this laboratory.[8]

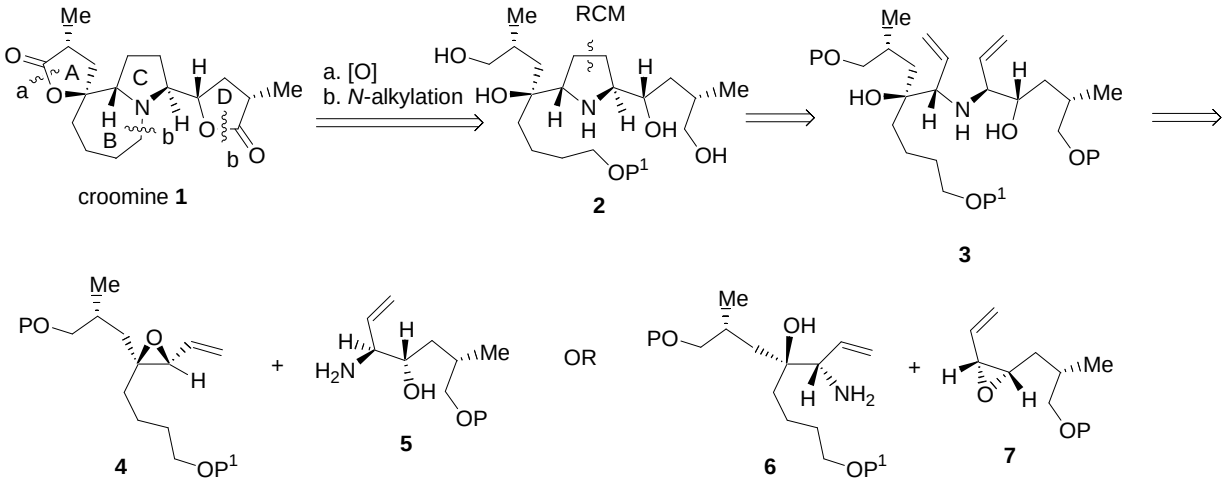
Scheme 2



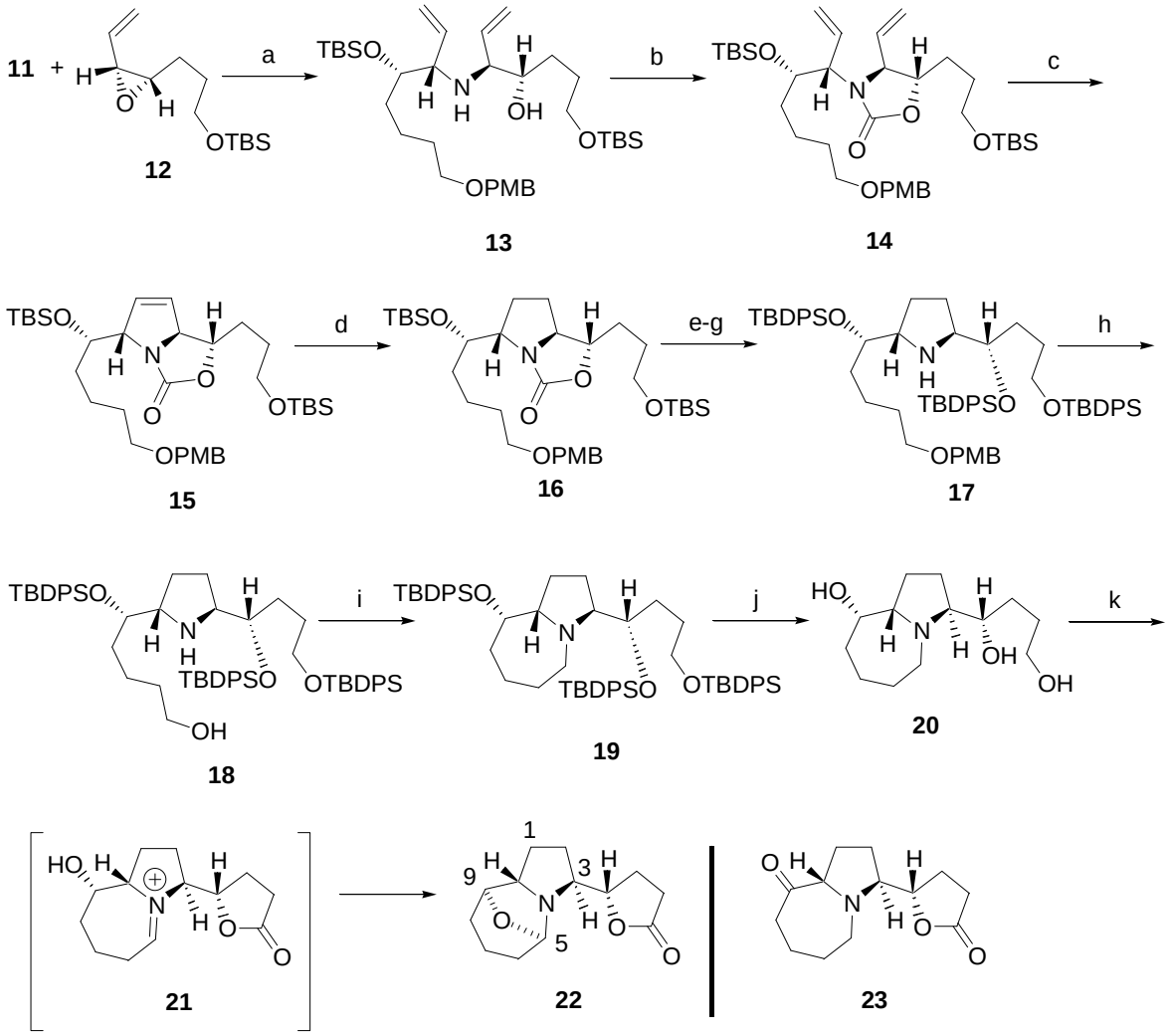
8 **9** **10**, R = H **11**, R = TBS

Reagents: (a) aqueous ammonia (28%), 110°C, 30 min, microwave heating (98%). (b) TBSCl, imidazole, MeCN, RT (85%).

Scheme 1. Retrosynthetic analysis of croomine (**1**).



Scheme 3



Reagents (a) LiOTf, CH_3CN, 130 °C, 4 d (95 %); (b) triphosgene, NEt_3, CH_2Cl_2 -40 °C (84 %); (c) Grubbs' cat., CH_2Cl_2, reflux, 7 d (93 %); (d) Pd/C, H_2, EtOAc, RT, 1 h (95 %); (e) *n*-Bu_4NF, THF, RT (100 %); (f) NaOH, MeOH, H_2O, 100 °C, microwave, 90 min (93 %); (g) TBDPSCl, imidazole, CH_3CN, 75 °C, 2 d (81 %); (h) CAN, CH_3CN, H_2O, CH_2Cl_2 (93 %); (i) PPh_3, CBr_4, NEt_3, 0 °C to RT (81 %); (j) HCl (38 %), MeOH, $CHCl_3$, 90 °C, 3 d (84 %); (k) TEMPO, BAIB, AcOH, RT (28 %).

Heating a mixture of **11** and **12** and lithium triflate (1.5 equiv) in acetonitrile solution at 130 °C for 4 days in a sealed tube provided the amino alcohol **13** (78%, ee estimated *ca* 95% due to removal of most of the undesired enentiomers of **11** and **12** as the diastereomer of **13**, but not determined) and its diastereomer (not shown, 17%) that were readily separated by column chromatography (Scheme 3).[6] The latter compound arises from the reaction of *ent*-**11** with **12** and **11** with *ent*-**12**. Treatment of **13** with triphosgene at –40 °C in the presence of base (Et_3N) gave the oxazolidinone **14** in 84% yield, along with an aziridine (not shown, 14%) that arises from reaction of triphosgene with the secondary hydroxyl group of **13** followed by intramolecular S_N2 displacement by the nitrogen atom at the carbon bearing the activated hydroxyl. The low temperature was required to minimise the formation of this aziridine. The oxazolidinone **14** was treated under standard RCM conditions (Grubbs' 1st generation catalyst and high dilution in dichloromethane solution).[7,11] The reaction was slow requiring 7 days of heating at reflux and high catalyst loading (50 mol %), however the yield of the 2,5-dihydropyrrole **15** was excellent (93%). Catalytic hydrogenation of the alkene group in **15** smoothly gave the pyrrolidine **16** without loss of the PMB group. Attempts to remove the PMB group from the analogous tris-TBS analogue of **17** resulted in cleavage of the primary TBS group and hence **16** was treated first with tetra-*n*-butylammonium fluoride (TBAF) to give the corresponding diol, which upon base catalysed hydrolyses of the oxazolidinone group and finally *O*-silylation with *tert*-butylchlorodiphenylsilane (TBDPSCl) gave the pyrrolidine **17** in 75 % overall yield. The primary *O*-PMB group was removed under oxidative conditions using ceric ammonium nitrate (CAN) to give the primary alcohol **18** in 93% yield which was converted to the 1*H*-pyrrolo[1,2-*a*]azepine **19** in 81% yield under standard cyclization conditions.[8,12] Compound **19** was treated with aqueous hydrochloric acid to give the triol **20**.[13] Oxidation of this triol to give the corresponding keto-lactone **23** proved difficult. For example, the use of tetrapropylammoniumperruthenate (TPAP)/*N*-methylmorpholine-*N*-oxide (NMO), a reagent combination that we have used successfully before to prepare a lactone from a related 1,4-diol,[6] gave a mixture of products including ones that showed aldehyde signals in the ^1H NMR spectra. When the oxidizing system 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, catalytic)/*bis*-acetoxy iodobenzene (BAIB, stoichiometric)[14,15] was employed in acetic acid as solvent, the product **22** was isolated in 28% yield having a novel 5,9-epoxy-1*H*-pyrrolo[1,2-*a*]azepine tricyclic ring structure. This structure most likely arises from oxidation of the tertiary amine to the corresponding cyclic iminium ion **21** followed by ring closure through the secondary hydroxyl in the azepine ring. The structure of **22** was supported by COSY, ^{13}C/DEPT and HSQC NMR experiments and mass spectrometry.[14] The hemiaminal carbon (C-5) was evident as a methine carbon at 96 ppm in the ^{13}C/DEPT NMR spectra.

In conclusion, we have developed a convergent and asymmetric synthesis of the tricyclic B,C,D-ring core structure of croomine, using aminolysis reactions of chiral vinyl epoxides and the RCM reaction. We are currently refining this strategy and developing syntheses of compounds **4** and **5** with the view of preparing croomine in the near future.

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(11) *(1S,5S,7aS)-5-[(1S)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-[(methoxyphenyl)methoxy]pentyl]-1-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-5,7a-dihydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one* (**14**). The diene **13** (547 mg, 0.826 mmol) was dissolved in dry DCM (95 mL), then Grubbs' 1st generation catalyst (338 mg, 0.413 mmol) was added. The mixture was heated at reflux under N_2 for 7d then cooled, before all volatiles were removed *in vacuo* to give a black oil. The pure product was obtained by column chromatography (increasing polarity from 10 % to 40 % EtOAc in pet. sp. as eluant), which gave a black oil. This was dissolved in EtOAc (30 mL) and stirred with activated charcoal for 20 min to remove residual ruthenium, then filtered through celite. Evaporation of the filtrate afforded the title compound (485 mg, 0.785 mmol, 92.6 %) as a colourless oil. $[\alpha]_D^{26}$: -86 (c 1.0, $CHCl_3$). MS (ES+) *m/z* 634.5 (100 %) (M+1), HRMS (ES+) found 634.3975, calc for $C_{34}H_{59}NO_6Si_2$ 634.3959 (M+1). δ_H (300 MHz, $CDCl_3$): 0.04 (6H, s, $(CH_3)_2Si$), 0.05 (6H, s, $(CH_3)_2Si$), 0.86 (9H, s, $(CH_3)_3CSi$), 0.89 (9H, s, $(CH_3)_3CSi$), 1.34-1.96 (10H, m, H2', H3', H4', H1" and H2"), 3.44 (2H, t, *J*=6.6 Hz, H5'), 3.62-3.74 (3H, m, H1' and H3"), 3.79 (3H, s, OCH_3), 4.24-4.30 (1H, m, H7*a*), 4.35 (1H, q, *J*=6.0 Hz, H1), 4.42 (2H, s, $OC\underline{H}_2Ar$), 4.54 (1H, app. t, *J*=3.9 Hz, H5), 5.85-5.92 (2H, m, H6 and H7), 6.86 (2H, d, *J*=8.7 Hz, 2 x ArCH), 7.25 (2H, d, *J*=8.7 Hz, 2 x ArCH). δ_C (75 MHz, $CDCl_3$): -5.4 (q, $(CH_3)_2Si$), -4.6 (q, CH_3Si), -4.4 (q, CH_3Si), 18.0 (s, $(CH_3)_3\underline{C}Si$), 18.3 (s, $(CH_3)_3\underline{C}Si$), 22.2 (t, C3'), 25.8 (q, $(\underline{C}H_3)_3CSi$), 25.9 (q, $(\underline{C}H_3)_3CSi$), 27.9, 29.9, 31.9, 33.6 (t, C2', C4', C1" and C2"), 55.2 (q, OCH_3), 62.3 (t, C3"), 70.0 (t, C5"), 70.6 (d, C7*a*), 71.0 (d, C5), 72.5 (t, $O\underline{C}H_2Ar$), 73.3 (d, C1'), 82.0 (d, C1), 113.7 (d, 2 x ArCH), 129.2 (d, 2 x ArCH), 129.6, 132.2 (d, C6 and C7), 130.8 (s, ArC), 159.0 (s, ArC), 162.4 (s, C3).

(12) *(3S,9S,9aS)-9-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-[(1S)-1,4-bis[[(1,1 dimethylethyl)diphenylsilyl]oxy]-butyl]-1H-pyrrolo[1,2-a]azepine* (**19**). The amino alcohol **18** (727 mg, 0.744 mmol) was dissolved in DCM (60 mL), then the solution was cooled to 0 °C. Carbon tetrabromide (604 mg, 1.828 mmol) and triphenylphosphine (475 mg, 1.828 mmol) were added, then the mixture was stirred at 0 °C for 10 min, before triethylamine (3.70 g, 36.56 mmol) was added. The mixture was stirred at 0 °C for 5 h, then left to stand at 4 °C for 20 h, then stirred at RT for 24 h. The mixture was poured into water (50 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a black semi-solid. The pure products were obtained by column chromatography (increasing polarity from 5 % to 25 % EtOAc in pet. sp. as eluant), which gave the title compound (451 mg, 0.470 mmol, 63.2 %) and the partially stable bromide intermediate. The bromide intermediate was dissolved in DCM (10 mL) and triethylamine (5 mL), then heated at reflux for 3 h. Work up and column chromatography as described above gave further title compound (128 mg, 0.134 mmol, 17.9 %, total yield 81.1 %) as a colourless oil. $[\alpha]_D^{24}$: -35 (c 1.28, $CHCl_3$). MS (ES+) *m/z* 958.6 (100 %) (M+1), HRMS (ES+) found 958.5452, calc for $C_{61}H_{80}NO_3Si$ 958.5446 (M+1). δ_H (300 MHz, $CDCl_3$): 1.07 (9H, s, $(CH_3)_3CSi$), 1.11 (18 H, s, $(CH_3)_3Si$), 0.80-1.80 (13H, m, H1, H2, H6, H7, H8a, H2' and H3'), 1.84-2.00 (1H, m, H8b), 2.34 (1H, dd, *J*=13.2, 9.0 Hz, H7a), 2.55 (1H, dd, *J*=13.5, 6.6 Hz, H7b), 3.10-3.20 (1H, m, H9*a*), 3.28-3.36 (1H, m, H5), 3.50 (2H, t, *J*=6.0 Hz, H4'), 3.76-3.84 (1H, m, H9), 3.84-3.92 (1H, dd, *J*=7.2, 3.0 Hz, H1'), 7.28-7.44 (18H, m, SiPh), 7.58-7.73 (12H, m, SiPh). δ_C (75 MHz, $CDCl_3$): 19.2 (s, $(CH_3)_3\underline{C}Si$), 19.3 (s, $(CH_3)_3\underline{C}Si$), 19.5 (s, $(CH_3)_3\underline{C}Si$), 26.8 (q, $(\underline{C}H_3)_3CSi$), 27.1 (q, $(\underline{C}H_3)_3CSi$), 27.2 (q, $(\underline{C}H_3)_3CSi$), 25.0, 25.1, 26.2, 27.1, 28.1, 30.0, 34.1 (t, C1, C2, C6, C7, C8, C2' and C3'), 48.3 (t, C7), 64.2 (t, C4'), 66.2 (d, C3), 66.7 (d, C9*a*), 74.0 (d, C9), 76.5 (d, C1'), 127.4, 127.5, 129.4, 129.5 (d, SiPh), 134.2, 134.2, 134.2, 134.5, 134.6, 134.7 (s, SiPh), 136.0, 136.0, 136.0 (d, SiPh).

(13) *(3S,9S,9aS)-3-[(1S)-1,4-Dihydroxybutyl]-9-hydroxy-1H-pyrrolo[1,2-a]azepine* (**20**). The tri-*O*-silyl ether **19** (61 mg, 0.0636 mmol) was dissolved in $CHCl_3$ (0.5 mL), then MeOH (4.0 mL) and conc HCl (1.0 mL, 38 % w/w) were added. The mixture was heated in a sealed tube at 90 ^oC for 3d then cooled. The mixture was poured into ether (40 mL) and extracted with 1M HCl (3 x 15 mL). The combined aqueous extracts were evaporated to dryness *in vacuo* to give a gum. This was dissolved in water (2 mL) and applied to basic ion exchange resin (OH- form). Elution with water (50 mL) and evaporation of the eluant gave the title compound (13 mg, 0.0534 mmol, 83.9 %) as a pale brown gum. $[\alpha]_D^{22}$: -34 (c 1.3, MeOH). MS (CI+) *m/z* 244 (100 %) (M+1), HRMS (CI+) found 244.1916, calc for $C_{13}H_{26}NO_3$ 244.1913 (M+1). δ_H (300 MHz, $CDCl_3$): 1.30-2.10 (17H, m, H1, H2, H6, H7, H8, H2', H3' and 2 x OH), 2.85 (1H, ddd, *J*=12.3, 6.3, 2.4 Hz, H5a), 2.94-3.08 (2H, m, H3 and H5b), 3.29 (1H, td, *J*=6.9, 2.4 Hz, H9*a*), 3.38 (1H, ddd, *J*=9.0, 6.3, 2.4 Hz, H1'), 3.60-3.76 (2H, m, H4'), 3.94 (1H, br. d, *J*=6.9 Hz, H9). δ_C (75 MHz, $CDCl_3$): 22.9 (t, C7), 27.9, 28.9, 29.4, 30.1, 32.1, 34.8 (t, C1, C2, C6, C8, C2' and C3'), 52.5 (t, C5), 62.9 (t, C4'), 65.3 (d, C9*a*), 71.0 (d, C3), 72.6 (d, C9), 72.8 (d, C1').

(14) *(3S,5S,9S,9aS)-3-[(5S)-tetrahydro-5-oxo-2-furanyl]-5,9-epoxy-1H-pyrrolo[1,2-a]azepine* (**22**). The triol **20** (25 mg, 0.103 mmol) was dissolved in AcOH (2 mL), then TEMPO (5 mg, 0.032 mmol) and BAIB (113 mg, 0.35 mmol) were added. The mixture was stirred at RT for 24 h, then $Na_2S_2O_3.5H_2O$ (125 mg, 0.504 mmol) was added. After 20 min the mixture was poured into 5 % NH_4OH solution (40 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) filtered and evaporated *in vacuo* to give an oil. The pure product was obtained by column chromatography (2 % MeOH in DCM as eluant) which gave the title compound (7 mg, 0.029 mmol, 28.6 %) as a pale yellow semi solid. MS (CI+) *m/z* 238 (100 %) (M+1). δ_H (300 MHz, $CDCl_3$): 0.80-2.00 (10H, m, H1a, H2, H6, H7, H8 and H4'a), 2.00-2.14 (1H, m, H1b), 2.25 (1H, dddd, *J*=12.6, 8.1, 6.9, 5.7 Hz, H4'b), 2.53 (1H, dd, *J*=9.6, 3.3 Hz, H3'a), 2.55 (1H, dd, *J*=9.6, 0.9 Hz, H3'b), 3.02 1H, ddd, *J*=10.2, 7.5, 5.4 Hz, H3), 3.46-3.80 (1H, m, H9*a*), 4.02 (1H, d, *J*=1.5 Hz, H9), 4.37 (1H, dt, *J*=7.8, 7.2 Hz, H5'), 4.82 (1H, s, H5). δ_C (75 MHz, $CDCl_3$): 16.8 (t, C7), 25.4 (t, C4'), 28.8 (t, C3'), 28.9, 29.2 (t, C6 and C8), 31.5 (t, C2), 31.6 (t, C1), 68.7 (d, C9*a*), 70.9 (d, C3), 78.9 (d, C9), 85.3 (d, C5'), 96.0 (d, C5), 177.0 (s, C2).

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